ATHOPHYSIOLOGY IN *Surgery*

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To

I S Ravdin

Preface

This book had its inception four years ago At that time an invitation from the publishers to assemble a volume in the field of surgical physiology was at first declined However the invitation began its subtle ferment, and I presently found myself examining existing pertinent publications with increasing interest It gradually became apparent, to me that existing works on surgical physiology perhaps *did not present the available material as one felt it might most effectively* be utilized Therefore when an adroitly conceived third prompting note arrived, I signed a contract for a manuscript to be delivered at what proved to be an exceedingly optimistic date

The next step was to impose upon about a dozen friends asking each to suggest ten areas which he felt should be covered in a surgical physiology This they very kindly did *and there was a remarkable unanimity in their replies For the most part the subjects suggested comprised the standard work-a-day physiology* of surgical practice and such material was utilized as the central core of the "practical material of the volume

Nevertheless to have confined the volume solely to what was considered "standard" surgical physiology would have been to deny oneself the anticipation of constructing a work which might more accurately supply the advanced needs of the contemporary surgeon It was felt that the striking reapproachment that *had recently come about among the disciplines of anatomy, chemistry internal* medicine, microbiology, pathology, physics physiology, and surgery should be reflected in the volume in a functional way Therefore many collateral subjects not usually considered as representing 'surgical' physiology have been included

Guiding Philosophy One major aim was to construct a work which would represent a fusion of medical" with "surgical' physiology Certainly the surgeon has in recent years become much more of an internist and internists are now *frequently in the operating room and surgical suite* A second objective was to emphasize the fundamental unity of the human organism which is achieved through three major coordinators the nervous system the circulatory system, and the endocrine system Third, the intent was to distill the physiologic information in such a way as to bring the applicable material to bear directly at the patient care level in most instances Numerous case studies have been used to further cement this union between physiology and daily practice

Selection of Material One of the *more difficult problems was that of selecting* the material to be used once the over all outline had been constructed As the volume was to run to some 500 printed pages, not counting illustrations, some process of selection was essential to achieve a balanced work.

The following criteria for selection were applied (1) Did the material bear directly upon the care of the patient? (2) Did it represent information which while as yet not immediately "practical' would prepare the reader to utilize advances that were likely to develop in the next decade? (3) *Did it afford an* opportunity to achieve correlation to emphasize that all physiologic activities are interrelated and to provide a balanced volume?

Treatment of Material A matter of genuine importance, always, is that of deciding upon the method of presentation of material The liberal use of diagrams, along with the aforementioned use of case studies, was conceived of as a unifying framework into which the physiologic principles might be drawn

The use of the English language was also given much thought One has but to enjoy the graphic case reports and editorials of many British writers, as well as those of a few journals in the United States, to appreciate the solid impact of the vernacular If in describing the physiologic factors involved in the case report the writer can make the reader remember the patient he saw day before yesterday, then the reader will remember the physiology involved Therefore, since the British themselves flex the language to achieve realistic clarity, it was felt that an American might be permitted a similar—though of course less extensive—freedom

The Problems and Rewards of Single Authorship Single authorship books of this length are less prevalent than they once were, though there are indications that the pendulum is swinging back a bit There is the question of the thoroughness with which one individual can write about multiple fields of endeavor For could not specialists in hematology, neurosurgery, and cardiology discuss coagulation defects, increased intracranial pressure, and interventricular septal defects in much greater detail? They doubtless might—but is it greater detail that the general surgeon needs? Or is it a concise summary of the essentials in a given field that are required, not for the practice of that specialty, but for the practice of general surgery? The general surgeon, writing for general surgeons, has the definite advantage of seeing the problems in the perspective of the general surgeon The inclusion of much extraneous material is thus avoided

It was noted at the beginning that this book has been long in the writing Or, more accurately, the final manuscript has been long in delivery to the publisher For several early chapters have been completely rewritten, not to mention repeated drafts of all chapters And herein lies a major problem of single authorship, namely, that of keeping the earlier chapters up to date as the later ones are completed Even so, despite the extra work entailed in rewriting, the long period of gestation has been good for the maturity of the volume Looking back, the earlier chapters were later revised because the author had considerably broadened, deepened, and extended his knowledge and experience in the field For once one is aware that he is to write on a particular subject, every patient, publication, and conversation becomes as grist to the mill As he turns his full attention to a given disease process, he views the problems with an intensity and critical perception that were often lacking before

Another reward of single authorship is that of knowing the volume from beginning to end This awareness makes for better correlation and fusion of the many subjects considered Furthermore, it vastly increases the range of medical interest of the writer, thus enhancing the flavor of everyday surgical practice For, of course, the value of a knowledge of physiology, of "how it works", is to set the surgeon free from the shackles of the unknown If in addition to technic he learns also what can be done—and what must *not* be done—to cure the patient physiologically, he can view and enjoy work-a-day practice with a most satisfying perspective Knowledge promotes freedom of action

Contents

The first ten chapters deal with the physiology of injury, body fluid physiology, surgical nutrition, connective tissue, wound healing and homotransplantation,

thermal burns the etiology, spread, and control of cancer radiation and radioactive isotopes, surgical enzymology and the biology of aging And these chapters serve as an introduction to the consideration of diseases of the various organs which follows in the next eleven chapters. The chapter on injury begins with a highway accident and concludes with a consideration of the metabolic response to trauma The chapter devoted to body constituents relates both normal and abnormal electrolyte metabolism, with some concrete suggestions as to therapy In each of the other chapters the physiologic implications and indications in therapy are touched upon

The eleven chapters dealing with surgical diseases of different organs usually begin with a brief survey of normal physiology and then proceed to pathophysiology and the therapeutic problems involved

It was not easy to decide whether the material concerning the circulation should be divided into three chapters or be included in one After much vacillation it was included in one with the objective of emphasizing the unity of the physiologic processes involved

Illustrations Particular care and emphasis have been devoted to the illustrations Many of the composites of diseases affecting particular organs were meticulously constructed by Dr Jorge A Rodriguez The extensive illustrative material has had as its special purpose the emphasis of the more practical clinical considerations

References Much reflection was given to the problem of how to handle the references Of the several thousand sources consulted in the over all preparation of the volume a great majority might very legitimately have been included At first it was felt that a comprehensive list should be appended at the end of each chapter Later it was felt that a minimum number should be used Finally, a middle course was followed First sources actually quoted had obviously to be included Second original articles were listed when feasible Not all of these could be verified with the facilities available to us and in some instances a simple statement of "not read" has been employed Even so prolonged tedious effort has been expended in the pursuit of recording references accurately Third, a few general review references in each field have usually been listed

It is still a matter of regret nevertheless that space could not permit the listing of many fine articles which were quite pertinent to the discussion but which were not needed and were in the end not used In amassing information of the range and type included in this book one comes to know, in a very gratifying way the minds and outlook of a great many investigators and clinicians

Acknowledgements

The opportunity to express appreciation to one s friends and associates is always one of the happier moments to be realized in writing a book. My first acknowledgement must be to my wife for her understanding and forbearance and to my small children for leaving their father s papers alone

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Chapter 1

The Physiology of Injury

The Management of Acute Trauma

The management of trauma is traditionally the responsibility of the surgeon And yet a surprisingly large number of surgeons complete their training and begin practice having had remarkably little contact with the severely injured Admittedly, these cases are not only inordinately demanding of time and skill but are also likely to require a prolonged period of hospitalization Even so, there is a rich satisfaction in acquiring the over all competence required to maintain "life limb, and happiness' for a man who has sustained multiple gunshot injuries of the chest, abdomen and extremities or for the woman badly injured in a car wreck It is one thing to perform a routine cholecystectomy or colon resection at 8 o clock in the morning—and it is quite another thing to admit at midnight a patient in shock from multiple stab or gunshot wounds to initiate resuscitative measures to stabilize common fractures to aspirate or operate for pericardial tamponade or for other intrathoracic hemorrhage, to repair a bronchus to explore the abdomen, close perforations of the small bowel or stomach perhaps to exteriorize large bowel, repair kidney or bladder remove the spleen, and ligate bleeding vessels, or to perform the required primary end to-end anastomosis of a severed popliteal artery to save the extremity (Fig. 1) Nevertheless, not until the senior resident can perform these measures, *in the order of physiologic urgency* (Fig. 2), is he properly prepared to manage casualties. He achieves the necessary information and poise through technical practice and by acquiring a basic knowledge of the physiologic requirements involved in different types of injuries

It is the purpose in this chapter to present some of the physiologic considerations attendant upon trauma and convalescence We shall begin with an illustrative annotated case study, followed by a brief survey of the principles of trauma management The general systemic response to injury is then reviewed after which the metabolic reaction to operation is detailed The discussion of the systemic response will consist to a considerable extent of the general alterations which occur and which can be grossly observed by the clinician, especially with the aid of various commonly used clinical measurements The review of the neuroendocrine response to trauma will, in contrast involve a descent into the more subtle functions of the organism, functions described in terms of laboratory measurements but functions which make possible the more gross alterations observed clinically The metabolic processes that are set in motion by a major injury involve not only all organs and all cells but doubtless the ultimate components of the cells themselves

A Patient and An Injury

CASE STUDY J T, a 62 year old man, had bought his weekly groceries on Saturday evening at the general store and was trudging back up the highway on his way home when he was struck by the trailer of a passing log truck. He was brought within the

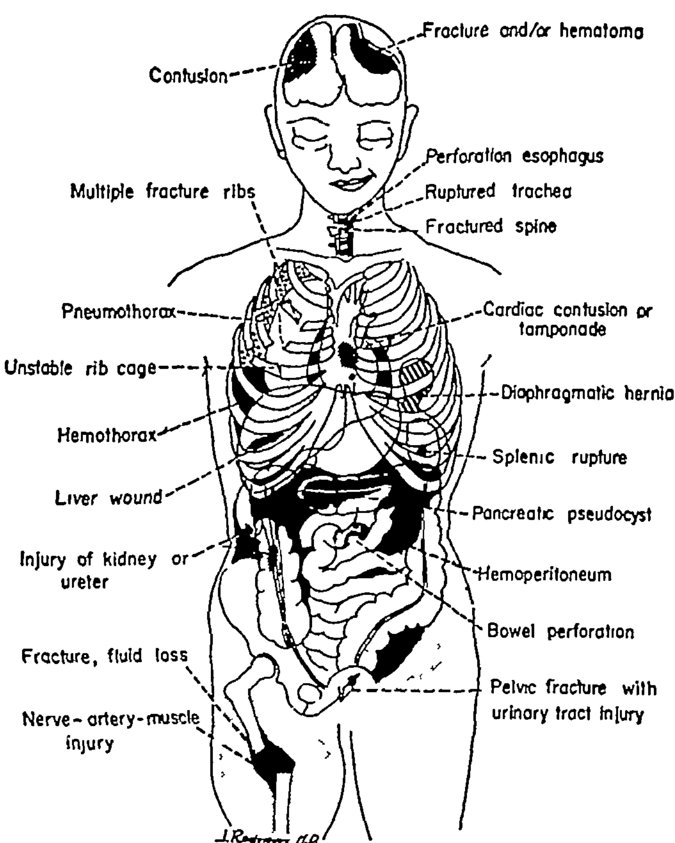


Fig 1 Shock following trauma can be due to many factors



Fig 2 Gunshot wound of the face The immediate and basic physiologic problems are those of restoring the blood volume and of providing a dependable airway by tracheostomy All else is of secondary importance

hour to the University Hospital, ·
was found to be comatose and in de·
The *coma* was considered to be due
in part, to the obvious head trauma,
with contusion or hemorrhage (C
appeared more likely, in the ab
localizing signs, respiratory rate ·
The *shock* was considered to be du·
to the head injury but also to flu
around the multiple fractures of
bones, to possible intra-abdominal
rhage, and to defective pulmonary
tion An infusion of dextran was beg
blood was being prepared, a trach
was performed, and oxygen was ·
tered (To avoid difficulty with ty
crossmatching, the blood sample h
drawn prior to the dextran infusion
was no blood in the catheterized uri
men

Meanwhile, rapid *physical exa*
had shown no evidence of external
rhage As noted, fractures of the lo
were evident, a skull fracture proba
fractures with pneumothorax possi
intraabdominal injuries due to
trauma not excluded There was
dominal rigidity or blood in the
Possibly pertinent findings were a
verse linear skin abrasion over the r
guinal region and a right scrotal
which probably contained bowel

Roentgen examination of the sk
vealed a nondepressed fracture, whic
self did not require surgery, there
evidence of bleeding or loss of cerebr
fluid through the ears or nose, and th·
were equal and reacted to light Th
film disclosed several rib fractures (
there was no paradoxical motion) an
was a left pneumothorax which wa
aged by the introduction of an int
rubber catheter with underwater dr
Fractures of both femurs, the left til
the right humerus (compounded)
demonstrated However the fra
were all merely immobilized with th
plest means possible, no effort being
to apply special traction, to cast, or

these fractures in the comatose individual A lateral decubitus film of the abdomen revealed no free air or apparent fluid

RECAPITULATION AND FURTHER MEASURES By now the immediate and overriding emergency requirements had been met in this comatose and hypotensive patient A dependable *airway* had been achieved by tracheostomy and the circulating *blood volume* had been increased by the intravenous infusion of dextran, followed by whole blood as soon as typing and crossmatching were complete The lung volume and thoracic bellows had been examined and, while the chest was not crushed it had been found necessary to improve lung volume by treating the left pneumothorax with closed (underwater) drainage Therefore the patient was now moving an adequate tidal volume of air (though pulmonary edema might be interfering with gas exchange across the alveolar membrane) Second, the net effect of transfusion and improved respiration had been to restore the blood pressure to 90 mm Hg systolic. The hemoglobin and hematocrit values had been found to be relatively normal in this individual, but too brief a time had elapsed for the blood remaining in his circulation to have become diluted by extracellular water, even if blood had been lost into the abdomen from injury to one of the viscera (liver or spleen, especially) or around the various fractures which he had sustained (for from 250 to 300 cc of blood may be lost around each fracture of the femur and a lesser amount around those of other bones)

FURTHER PROGRESS Following the emergency resuscitation the patient emerged somewhat from his coma and while certainly not rational he at least gave evidence that he would probably regain consciousness in a few hours (and that craniotomy or burr holes for decompression would probably not be required) This was important for one did not wish to perform a laparotomy upon a patient who was still in coma, if this could possibly be avoided—and it was too early to exclude intra abdominal injury

With the tracheostomy functioning satisfactorily (it permitted an opportunity to aspirate tracheal secretions in the semicomatose patient, it diminished the respiratory effort required for respiration, and it diminished the anatomic dead space of the tracheobronchial tree), and with the blood pressure rise to above 90 mm Hg it was decided to move the patient from the emergency room to the surgical floor On the ward the abdomen was again carefully examined The fact that the blood pressure had responded rather promptly to improved pulmonary ventilation and limited blood transfusion rendered it unlikely that a significant volume of blood had been lost into the abdominal cavity or bowel, and it was still considered probable that the shock which he had exhibited had been due to the head injury, the pneumothorax, the numerous fractures and the loss of blood and extracellular fluid into the tissues surrounding the fractures The large right inguinal hernia which contained bowel and for which relatives stated he had never worn a truss was again noted, as was the inguinal abrasion. Peristalsis was barely audible, but the abdomen was not rigid It was difficult to evaluate tenderness because of his semicomatose state, but certainly the abdomen was not markedly tender Only gastric juice was aspirated through the Levin tube and microscopic examination of the urine removed at the time the Foley catheter was inserted had demonstrated no red cells Had there been red cells, an intravenous pyelogram and a cystogram would have been performed to examine for urinary tract extravasation If there had been serious injury to a kidney, ureter, or the bladder, early operation would have been necessary for repair and drainage since urine may have a very vicious effect upon body tissues outside the urinary tract itself (Fig 277)

Throughout the remainder of Saturday night the sensorium gradually cleared and the blood pressure was readily maintained above 100 mm Hg with a slow drip of blood.

He had been admitted to the hospital at approximately 10 o'clock Saturday evening, and by the next morning he appeared to be doing fairly well There was, however, concern over the fact that the early improvement in the sensorium had not continued to progress, and for this reason operation for definitive management of the fractures was further delayed Repeat roentgen examination of the chest indicated virtually complete re-expansion of the left lung Re-examination of the abdomen again indicated diminished peristaltic activity and possibly more tenderness than had been present the previous evening Even so, it was felt that this tenderness was not out of proportion to the muscle trauma that the abdominal wall had probably sustained, in view of the obvious abrasion in the right inguinal region, conservative management was continued, with heavy antibiotic coverage and continuous nasogastric suction It was noted, nevertheless, that the scrotal hernia was more tender, in that palpation here caused him to wince more than palpation of any other region of the abdomen He still was not sufficiently alert to answer to his name or to recognize members of his family

Late Sunday afternoon he took a turn for the worse, the systolic blood pressure declined to within the 90's, and an additional blood transfusion was given The pulse rate had increased to approximately 110 per minute and the rectal temperature was approximately 100 to 101° F These changes were of course disturbing but it was felt that, aside from the moderate hypotension, the alterations in the vital signs were perhaps not out of line with the amount of trauma which he had sustained—and that, indeed, the moderate decline in blood pressure might be due to a continued extravasation of blood and fluid into the tissues surrounding the fractures By midnight, though, it was found that the transfusion of blood would no longer readily maintain the blood pressure above shock level The hematocrit was repeated and it was 53 A small amount of norepinephrine was required to sustain the blood pressure, but no other change was noted by the examiners

By the Monday morning after admission matters had taken a rather drastic turn Within the period of an hour or so his temperature had risen to 104° F , the pulse rate had increased to 120, and the abdomen had become moderately distended and now exhibited generalized tenderness It was necessary to add several ampules of norepinephrine to each bottle of infused fluid to maintain the blood pressure above 90, and it was obvious that some further and quite serious diagnosis had to be considered The fever, the tender and distended abdomen, the fall in blood pressure, the rapid pulse, and the ever more tender hernia—these findings prompted us to explore the abdomen of this patient, who remained semicomatose No sooner had the peritoneum been exposed under local anesthesia than dark fluid showed through, and upon opening the peritoneum a considerable volume of dark, bloody and foul-smelling fluid escaped Gentle traction was exerted on the bowel entering the hernia, and there emerged a grossly gangrenous loop It was found that the 18-inch loop of small bowel contained in the right inguinal hernia was necrotic, due to the fact that the blow in the inguinal region had completely severed its mesentery There was no definite evidence that the bowel itself had been perforated by the injury, the mesentery had simply been mashed in two The gangrenous bowel was resected, but despite increased amounts of blood given postoperatively the shock was irreversible The patient lived only eight hours following surgery

Comment on Case

This particular case was chosen from among many because it exemplifies a number of physiologic variables which must be borne in mind in the management of a severely injured person First, it served to emphasize, again, that *the two most important considerations in the immediate emergency*

management of an injured person are those of maintaining adequate respiration and circulation

Second, this patient afforded an opportunity to emphasize the fact that shock may be due to many different factors, in addition to the obvious and always to be considered possibility of diminished circulating blood volume due to blood loss *per se* The likelihood that the shock was due, in part, to intracranial trauma had to be entertained, as well as the fact that the pneumothorax might be resulting in hypercapnia and anoxemia Moreover, the pneumothorax had produced a shift in the mediastinum (Fig 181) that could be interfering with the venous return to the right heart, further diminishing cardiac output We treated a patient with massive pyopneumothorax from a stab wound who had edema of the lower half of his body and the upper left portion of the body—but no edema of the upper right portion of the body, including the arm (Fig 208) When the massive right shift of the mediastinum had been corrected by the removal of 6 L of fluid from the left chest, the edema cleared within 24 hours It was considered probable that the left innominate vein and the inferior vena cava had been kinked by the mediastinal displacement, while the right innominate vein had not

Traumatic shock is occasionally due to cardiac contusion or to coronary thrombosis, and an electrocardiogram was made in the first case for that reason though it was within normal limits Moreover in any patient who is comatose one must consider the possibility of a cerebrovascular accident *Fat embolism* to the brain is also a serious complication in many traumatic injuries. The multiple and severe fractures which the patient sustained were more or less typical of those which one may anticipate in an automobile accident, and they in themselves were sufficiently extensive to have produced shock from the loss of blood and fluid into the surrounding tissues Only one of the fractures was an open or compound fracture, however, and bacteremic shock from that source seemed unlikely

Finally, the case emphasizes that despite the continued observation and the awareness that intra abdominal injury might have occurred, the extent of the intra abdominal pathology was not appreciated by the attending surgeons until the marked fall in blood pressure, with the increase in pulse rate and the spike in body temperature, suggested that peritoneal soiling had occurred This possibility was further supported by the moderate tenderness and rigidity which the patient gradually developed, despite the semicomatose state The point is made also that a great deal can be done with local anesthesia, for certainly no one wished to give this patient a general anesthetic, and the multiple fractures rendered it most difficult to use a spinal anesthetic

In conclusion, let it be noted that the mortality rate following severe traumatic injuries is high, particularly among the elderly This man, with the extent of injury which he had sustained, might have died from intracranial trauma, or from respiratory difficulties, had enough ribs been fractured to produce the very dangerous flail chest with paradoxical motion (Fig. 181), or from complications attendant upon the long siege of care for the fractures of the extremities, though fractures *per se* are surprisingly well tolerated. He could well have died from lower nephron nephrosis and uremia, fat embolism, infection other than that which occurred in the peritoneal cavity, or from entirely unanticipated complications which have a way of following in the wake of other serious diseases—such as cerebral hemorrhage pulmonary embolism, heart failure, or pneumonia

Clinical Recapitulation: Some Principles of Trauma Management

The physiologic requirements of the treatment of any particular case of trauma vary with the injury that has been sustained Therefore, every injured patient must have

a complete clinical examination, including the neurologic evaluation In intoxicated patients who have sustained stab or gunshot wounds, the nerve injuries are often missed until the postoperative recovery period The "simple" gunshot injury may consist of several slugs that have struck the patient and have gone in various directions At the writing there is a patient on our wards who was shot twice in the back with a 38-caliber pistol There were seven perforations of the small bowel, two of the stomach, a fracture of the left kidney and division of the right ureter, a vertebral fracture with spinal cord injury, and a fracture of the right radius He has a right ureteral fistula, but otherwise is doing well except for some paralysis of the right leg The point is, bullet wounds may cause an astonishing amount of damage

Full use should be made of routine roentgen studies of the head, chest, abdomen, and extremities and of radiopaque materials for urogram, cystogram, bronchograms, esophagram, and angiograms

If there is a *knife wound of the chest*, it may or may not have penetrated the diaphragm and injured abdominal viscera One can gain a reasonably good estimate of the probable distance which the knife penetrated if the length of the knife is known (which information the patient may or may not have gleaned in the emergency) and if the distance from the diaphragm at which the chest was penetrated is noted Actually, many knife injuries do not penetrate the body wall, but virtually all wounds that involve the abdomen are explored, at least to the extent of determining whether or not the peritoneum was penetrated Knife injuries of the chest *per se* need not be explored in the majority of instances Bleeding from a pulmonary vessel will usually cease, though blood may need to be aspirated from the chest several times Bleeding from a systemic vessel such as an intercostal artery, the internal mammary artery or, of course, the aorta will commonly not stop, and thoracotomy may be required Pericardial tamponade can be successfully managed by pericardicentesis in most patients who reach the hospital, repeated as necessary, occasionally thoracotomy is required. Air leaks are treated by aspiration or by underwater seal drainage Similarly, a bullet wound of the chest may not require exploration This is particularly true if there are wounds of both entrance and exit, and if it appears probable that the abdominal cavity has not been involved. Of course, one must always consider the possibility that, aside from leaks of air or blood which may have been produced through pulmonary injury, the esophagus may have been perforated or a major bronchus torn In brief, any structure which lies along the probable path of the bullet or knife may sustain damage and appropriate examination must be conducted to exclude or repair injuries which might otherwise result in death from infection This is especialy important in the case of injuries to the esophagus as it passes through the mediastinum Shotgun wounds of the chest, particularly if inflicted at close range, may require thoracotomy to remove wadding, clothing, and devitalized tissue, for otherwise empyema will often result

Bullet wounds of the abdomen should also be explored, since usually one or more of the viscera will have been seriously injured (Fig 1)

A definite routine of the operator's choice should be employed when exploring the abdomen, else injuries will be missed To begin with, adequate exposure will be necessary, and it might as well be obtained at the beginning without the subsequent delay of having to manipulate the drapes to extend the incision We have found a paramedian incision, usually on the right, a suitable one for this work The character of any fluid within the abdomen will be noted, for the presence of fresh blood renders it imperative that the site of hemorrhage be located, if for no other reason than to exclude perforation of a viscus If the injury is quite recent, a fecal odor suggests colon injury, if the injury is many hours old, small bowel contamination may also produce a foul odor

From the bacteriologic standpoint, the seriousness of bowel injury increases from the stomach downward. If it appears that there are perforations of the intestine and continuing hemorrhage is not serious, the bowel wounds should be taken care of first, to diminish further soiling as the gut is manipulated in the examination of other organs. The obvious perforations are closed or, if necessary, resected, and then the bowel is "run" from the stomach to the pelvic floor. Perforations of the posterior surfaces of unmobilized stomach, duodenum, and colon are especially apt to be missed. If there is any serious question regarding injury to the bowel below the pelvic floor, which can be suspected from the direction of the bullet wound or other injury and from rectal and sigmoidoscopic examinations which reveal blood, one must decide whether he will do a proximal colostomy and/or drain the perirectal space by perianal incisions below—or depend upon conservatism. As a rule, it is safer to perform a proximal colostomy, but regardless, I do not routinely drain from below. If a perforation is seen on one surface of the bowel or stomach, then one must look very carefully for a perforation on the other side. While tangential injury from a missile does rarely occur, it is hazardous to assume that this is the case until a careful search of the opposite side of the viscus has been made.

Following closure of all perforations of the bowel, with resection of unsalvageable portions, one may then turn attention to other organs. (He may have been forced to turn his attention to other organs earlier if loss of blood from these organs was a serious threat to the maintenance of an adequate blood pressure.) The other organs too must be examined in just as systematic a manner as was the bowel. I often begin by examining the spleen, chiefly because this organ is easily injured and is easily removed. Since it is not possible to suture the splenic capsule, the diagnosis of capsular damage is the indication for splenectomy. At the time the spleen is examined one may also examine the left kidney region for damage and the diaphragm for perforation, if he has not done this while examining the upper portions of the stomach. Defects in the diaphragm should be closed to prevent future herniation of abdominal viscera. Next, the liver is inspected and evidence of bile leakage or blood noted. If an injury to the liver is not a large one, it is usually a relatively simple matter to suture a bleeding point. Mattress sutures are employed. On the other hand, if a large segment of a lobe of the liver has been fractured or macerated it may be extremely difficult to stop hemorrhage. Major vessels within the substance of the liver can be ligated with suture ligatures, but once the capsule of the liver overlying macerated parenchyma has been lost, innumerable oozing points may render efforts at hemostasis quite exasperating. We examined this problem in the laboratory, following a fatal case of hemorrhage in which we had been unable to stop bleeding from the right lobe of a woman whose liver was crushed when she was pinned in a ditch by the bumper of a car. It was found that temporary occlusion of the portal vein had little effect upon bleeding from liver wounds inflicted in dogs, but that temporary occlusion of the gastrohepatic artery had a marked effect in diminishing this oozing and allowed a number of the bleeding points to clot. The use of heavy ("pistol") cautery was of some value in coagulating bleeding surfaces or in actually excising portions of the liver. Neither late hemorrhage nor biliary fistula occurred following the use of such cautery. Packing of the injured liver is often ineffective in controlling hemorrhage.

The *pancreas* may have been injured and, if so, the area should be drained.

Suitable evaluation of the status of the *urinary tract* should also be carried out. However, if there was no blood in the preoperative urine specimen and emergency intravenous pyelogram showed no extravasation of radiopaque medium from the kidneys, ureters or bladder, we do not routinely expose and directly visualize these

structures (A cystogram may be obtained by injecting Urokon through the indwelling Foley catheter) Conservatism is always advisable regarding removal of an injured kidney, for often it can be saved Moreover, the opposite kidney may have been damaged Recall that in a case cited above the left renal parenchyma was damaged but that the right ureter was later found to be severed This ureteral injury was missed at the original laparotomy and was discovered only when urine escaped through the drainage stab wound Since the right kidney eventually had to be removed, it was well that the injured left kidney had been conserved

Drainage is advisable in most instances where extensive damage has occurred It permits escape of blood, and overlooked pancreatic, biliary, urinary, or bowel injuries may be more readily diagnosed

Vascular injuries respond extremely well to competent management If several liters of blood (pumped in rapidly) have not raised the blood pressure of a patient with abdominal wounds, the abdomen should be promptly opened (if shock is present, little anesthesia is needed) and the bleeding controlled surgically, following hemostasis, the infusion of further blood may soon restore a stable and adequate blood pressure Intrathoracic hemorrhage can be followed by means of repeated chest x-rays and thoracenteses, but the possibility that the shock is due to pericardial tamponade in a penetrating injury should not be overlooked—a diagnostic pericardial tap is usually harmless and may be lifesaving Wounds of the mouth may require tracheostomy (Fig 2)

Above all, it is no longer permissible simply to ligate important arteries The ends can usually be debrided and anastomosed with a continuous over-and-over stitch If the divided ends cannot be pulled together, a venous graft, arterial homograft, or plastic vascular substitute can be used The results of primary suture of the femoral or popliteal artery are almost uniformly good, in our experience

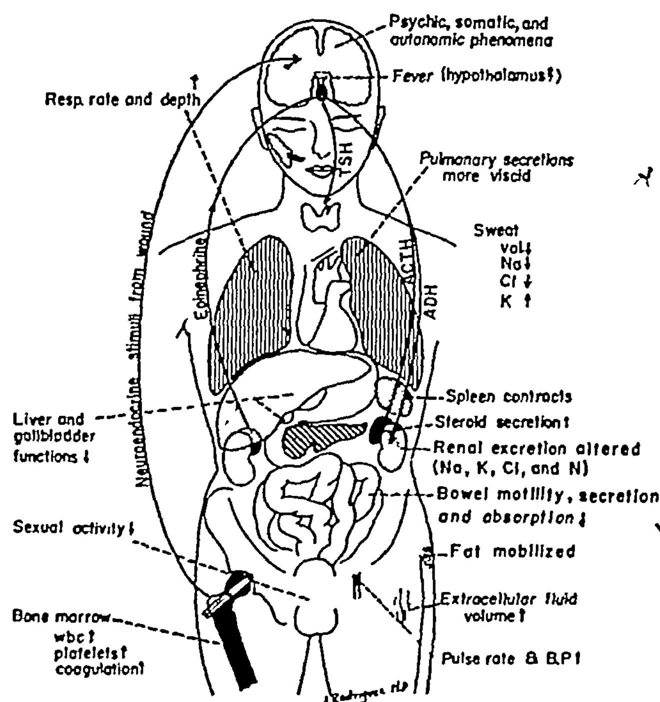


Fig 3 All organs participate in the stress response to anesthesia-operation or other trauma The diminished urine volume is one of the more conspicuous effects, associated with a retention of sodium and chloride and an excretion of potassium

Systemic Response to Injury: A Brief Survey

Every organ and virtually all cells of the body participate in the response to injury (Fig 3) and, up to a point, the magnitude of the physiologic response is proportional to the magnitude of the injury However, if the individual is chronically ill his response to a given operation will be less marked

THE CIRCULATION Major trauma produces a release of epinephrine and norepinephrine, which results in an increased rate and force of the heart beat and a further rise in blood pressure due to vasoconstriction The spleen contracts and makes available additional red blood cells for the general circulation Nevertheless, if these sympathomimetic effects on the peripherovascular bed are outweighed by blood loss, then the blood pressure will fall

The general state of the circulation, as reflected in the blood pressure, is usually taken as a gauge of the magnitude of the injury or of the volume of blood loss A

man in profound shock following trauma will usually have suffered serious damage. Yet, if a simple vascular injury has merely resulted in massive blood loss—there being little additional tissue injury—recovery may be prompt with adequate blood transfusion.

Irreversible shock has been considered by Shorr and his associates[26] to be due to prolonged hepatic anoxia which results in the elaboration by the liver (and muscles) of abnormally large quantities of a substance they termed a vasodepressor material (VDM) later tentatively identified as ferritin. In their view, a certain amount of VDM is ordinarily produced by the liver but the normal liver is also able to detoxify this substance. Moreover, an opposing factor, vasoexcitatory material (VEM) produced by the normal kidney, tends to elevate the blood pressure. As tissue anoxia continues, increasing amounts of VDM and decreasing amounts of VEM are produced and irreversible shock results.

Regardless of the ultimate explanation of irreversible shock—and we believe that the problem is still an unsolved one—the experience gained during the Korean War proved that many cases of shock which might previously have been considered "irreversible" actually were reversed with massive transfusions of blood ranging up to 25 or more pints. In all branches of surgery, civilian and military, the experiences of the last two decades have emphasized with increasing force the need for truly adequate blood replacement (Fig. 134).

As opposed to shock, there is at times a *hypertensive response to trauma*. We have encountered this phenomenon in a few patients who had sustained thermal burns of relatively mild extent and who were not oliguric. The hypertension appeared during either the first or the second day following the burn and often persisted for almost one week before gradually subsiding. A similar response was observed occasionally in recently wounded soldiers in Korea, the hypertension persisting until an anesthetic was given. It was found that Regitine depre[...] and that hexamethonium abolished, th[...] pertensive response.[17] Recent studies o[...] secretion of epinephrine and norepineph[...] during trauma further emphasize the [...]sible rôle of the adrenal medulla in the [...]esis of this type of hypertension.[11]

Abrupt hypertension is occasionally [...]countered following operation and in o[...] circumstances. For example, a certain n[...]ber of patients develop arterial hyperten[...] following a portacaval anastomosis, th[...] it is not clear whether this is due to alt[...] renal, hepatic or adrenal function. Furt[...]more, patients with oliguria or anuria [...] to renal damage commonly develop a de[...] of hypertension. Resection of coarctatio[...] the aorta may be followed by tempor[...] increased hypertension, perhaps the r[...] of adrenal medullary secretion.[25]

Lastly, although a great many o[...] facets of altered circulation in injury c[...] be discussed—among them cardiac funct[...] arteriolar changes, capillary permeab[...] and alterations in red cell mass and pla[...] volume—further discussion will be lim[...] to mention of the impaired quality of [...] *postural circulatory reflexes* during co[...]lescence. All clinicians have noted that [...] patient who has recently been operated u[...] is unstable on his feet on first standing a[...] several days in bed. This is due to the [...] that not only does the circulating bl[...] volume quantitatively diminish follow[...] bed rest but also to the fact that the sp[...] with which the circulatory reflexes b[...] about a redistribution of the blood vol[...] upon standing is diminished. The pheno[...]non of orthostatic hypotension often oc[...] following extensive sympathectomy for [...]pertension, and the patient may actu[...] faint because of cerebral ischemia, the [...]sult of pooling of blood in the lower [...]tremities and in the splanchnic area.

In the healthy subject the circulatory adjustments to postural changes occur [...] rapidly that hypotension does not occur [...] was shown by Mayock and others[22] that [...] circulatory abnormalities exhibited

gical patients during convalescence could be minimized by an aggressive feeding program which reduced the usual negative nitrogen balance

THE RESPIRATORY SYSTEM The ways in which the respiratory system reacts to a distant injury are not so well documented as are those of the circulatory system, but few doubt that the lungs and bronchi participate For example, the patient often appears to exhibit a more viscid and tenacious sputum postoperatively, even when spinal anesthesia was used Sporadic workers have attempted to demonstrate chemical and other alterations in the tracheobronchial secretions postoperatively, but by and large these efforts have not been notably successful Yet, there can be little question that the cells lining the respiratory tract are affected by the manifold physiologic responses to trauma

Following major surgical procedures, various degrees of pulmonary atelectasis may result in defective pulmonary ventilation and oxygenation of the blood This fact has long fostered an insistence upon deep breathing and coughing in the early postoperative period, plus the use of nasotracheal catheter suction to remove secretions and prevent bronchial occlusion (Fig 184) The cyanosis that many patients exhibit postoperatively is probably due less to inadequate total ventilatory exchange than to inadequate ventilation of multiple smaller bronchi occluded by secretions, blood continues to flow through these poorly ventilated lung segments but is not oxygenated, resulting in cyanosis due to this "functional shunt" In effect, this is the cyanosis which results from a pulmonary arteriovenous (A-V) fistula, for here, too, pulmonary arterial (venous) blood passes to the pulmonary veins and thence to the left atrium without having been oxygenated In the event of blood's passing through the atelectatic or nonventilated lung, it does pass through the capillary bed, to be sure (in contrast to the pulmonary A-V fistula), but it is still not oxygenated and the carbon dioxide contained in the blood flowing through the atelectatic lung is not excreted The *vital capacity* is diminished in most patients following operation

More recently an additional type of measurement has been employed which promises to be useful in further analyzing the effect of anesthesia and operation upon lung function This is the study of *pulmonary compliance* Simply put, the compliance of the lung is measured in terms of the amount of positive pressure (exerted through the tracheobronchial tree) required to expand the lung In the normal lung this is, of course, a very small positive pressure However, following the use of most types of inhalation anesthetic agents—and presumably following injury and in cardiac failure—pulmonary compliance is reduced, the lung becomes less distensible and hence less efficient in achieving adequate respiration Although the methods available for measuring compliance clinically are still crude, it is likely that much useful information will be derived from such studies performed before and following operation Compliance represents, in essence, the elasticity of the lungs, and it is reflected in the elastic recoil of the lung during expiration

Postoperative pulmonary edema, whether due to excessive salt infusion or other causes, is a threat to effective ventilation and to the exchange of gases across the alveolar membrane

THE GASTROINTESTINAL TRACT The mouth is dry and the patient thirsty when shock follows blood loss Moreover, the volume of gastric secretions is diminished during stress, and following operation the volume of fluid which can be aspirated from the small bowel through an inlying Miller-Abbott tube is diminished[13] One practical implication of the latter is that the surgeon need not be concerned if the drainage volume is small, so long as the abdomen is not distended, the bowel is in all likelihood adequately decompressed and the anastomosis protected

Intestinal motility and the absorption of

various substances are altered by injury, and postoperative intestinal dysfunction remains a major source of morbidity in surgical practice

THE LIVER, GALLBLADDER, SPLEEN, AND PANCREAS Numerous studies over the years have indicated various minor alterations in liver function following the insult of anesthesia and operation.[70] Yet the tremendous functional reserve of the liver usually precludes a serious failure in any of its multiple activities, though in the occasional patient acute liver failure may result in death. The liver is the center of a major segment of the metabolic activity of the body (Fig 73) and patients with liver disease, particularly those with homologous serum jaundice or other hepatitis are notoriously poor risks for major surgery. Most important, the liver is sensitive to anoxia and defective anesthesia and shock must be avoided

Gallbladder function has been shown to be affected by acute trauma.[16]

The spleen also has long been known to participate in the physiology of stress in animals, since the release of epinephrine and norepinephrine results in a contraction of this organ to force additional red cells into the general circulation to assist in meeting the emergency. Any medical student may inject a small amount of epinephrine into the splenic artery of the dog and observe the rapid reduction in size and increase in firmness of this organ. However, the increment in red cell mass supplied by splenic contraction in man is probably not very significant

The more subtle role of the spleen with respect to regulation of the numbers of platelets, red cells and white cells following trauma may be more important in man than is splenic contraction. Blood coagulability is increased following operation, perhaps in part the result of an increase in platelet concentration

The bone marrow participates in stress but these functions have not yet been clarified. The white blood cell and platelet counts increase, but the eosinophil count decreases.

The pancreas has a role in the stress of anesthesia and operation, both endocrine and exocrine. Following massive injury, as for example in thermal burns, the patient may exhibit an elevated blood sugar level, a diabetic type glucose tolerance curve, and glycosuria. It is possible that this is due to the diabetogenic effect of the increased amounts of adrenocortical hormones in causing "insulin resistance," but the possibility of reduced insulin production cannot be excluded. Unfortunately, there exists as yet no simple way in which to measure insulin concentration in the blood. Biologic assays are quite too insensitive to study minor changes in endogenous insulin production

The serum amylase level may be diminished following traumatic injuries which do not involve the pancreas, but it is usually increased in blunt (or other) trauma to the organ itself

THE NERVOUS SYSTEM, THE MUSCLES, THE ENDOCRINE GLANDS, AND THE KIDNEYS These organs are mentioned in this particular location merely to indicate the general nature of the response to stress. The nervous system participates profoundly in the stress response—through hypothalamo-hypophyseal release of adrenocorticotropic hormone (ACTH), through altered psychic and motor functions and through the sympathetic and parasympathetic discharges. The muscles comprise the large portion of the metabolically active lean tissue mass and hence must be considered the site of a major portion of the metabolic response to trauma. The rôle of other endocrine organs and of the kidneys will be described in detail below for the changes in the function of these organs constitute major features of the reaction to operation

The Metabolic Response to Acute Trauma and to Anesthesia-Operation

The Neuroendocrine Response (Fig 4)

The assault of anesthesia and the operation, or of other trauma, releases

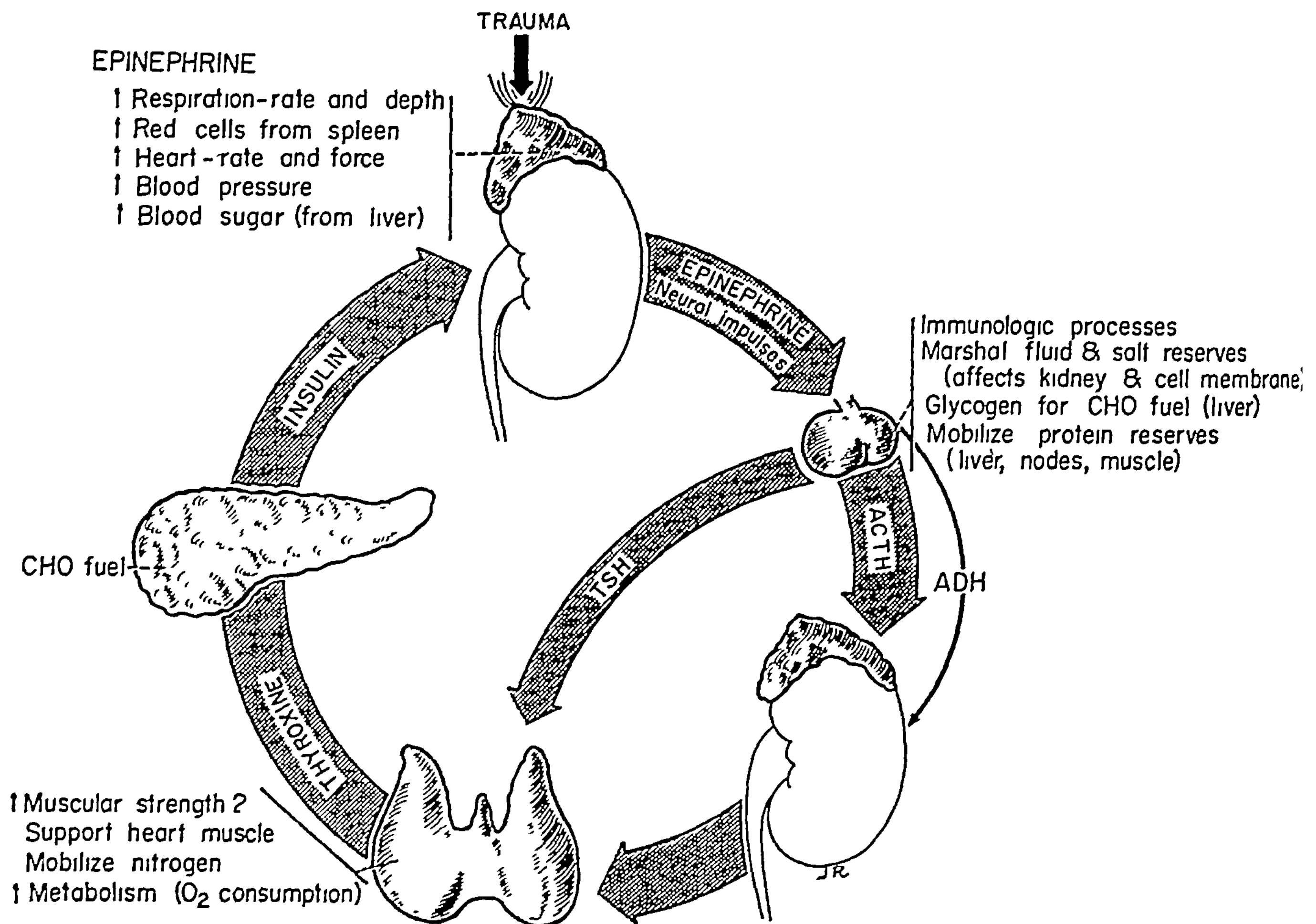


Fig. 4 In this diagram the interrelationships between the effects of the various endocrine organs are emphasized Elaborate systems of checks and balances exist among hormonal functions (Modified from HARDY, J D *Surgery and the Endocrine System,* Philadelphia, W B Saunders Company, 1952)

both neural and humoral, which cause the adrenal medulla to secrete increased amounts of epinephrine and norepinephrine, with their sympathomimetic effects It was demonstrated by Cannon[4] in 1914 that injury or the threat of injury to an animal resulted in a neuroendocrine response which prepared the animal for defensive activity or for flight These studies were centered chiefly upon the rôle of the adrenal medulla, but the rôle of the nervous system was not ignored This problem has recently been reexamined by Hume[15]

Simultaneously with the increased secretion of epinephrine, the pituitary is caused to release at least three important hormones. adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), and antidiuretic hormone (ADH) In turn, the ACTH stimulates the adrenal cortex to secrete increased amounts of its various steroids with their manifold effects upon a great variety of body processes, the TSH probably stimulates the thyroid to increased activity, though the particular rôle of an increased thyroid activity in the stress response still cannot be precisely defined at this time, and the increased secretion of ADH by the posterior pituitary results in the retention of water, due to an increased reabsorption by the renal tubules ADH may under some circumstances increase the excretion of sodium and chloride by the renal tubules, but the net effect of the interaction of this hormone with the adrenocortical hormones is usually that of a temporary retention of sodium, chloride, and water, but an excretion of potassium

Teleologically speaking, it may be that the retention of salt and water is to augment the extracellular and plasma volumes as a defense mechanism against injury and blood loss

It has been seen that the epinephrine liberated in stress has effects upon the rate and depth of respiration, upon the rate and force of cardiac muscular contraction upon circulatory vascular reflexes upon the rate of body metabolism and upon the release of additional red cells from the spleen It promotes glycogenolysis in the liver to provide an immediately utilizable source of fuel (glucose) for the body The more sustained elevation of the blood sugar level that may be met in chronic trauma burns and sepsis is perhaps the result of the antagonistic effect of adrenocortical hormones to that of insulin and their conversion of amino acids to glycogen

So much for the general picture How specifically is activation of the neuroendocrine response initiated?

Activation of the Stress Response

In pursuing this discussion of the pituitary adrenal interrelationships it is of interest to note that the stress reaction may be initiated by a considerable variety of stimuli other than traumatic injury For example, minor but definite stress responses may be obtained from psychic or emotional insult, from acid loads from the "dumping syndrome" which follows subtotal gastric resection (actually shock?), from fever infection, and many other factors. Thus, the cycle of the stress reaction (Fig. 4) may be initiated at any of several points For example, hyperthyroidism may be precipitated at first by emotional stress but once the disease has developed the thyroid hormones further exaggerate the emotional turmoil The absence of a sufficient quantity of insulin results in stress as does the presence of too much insulin, with convulsions and coma The psychic factors produce the stress reaction through the neurohumoral chain extending from the cerebral cortex to the hypothalamus, to the pituitary, and to the adrenal cortex, on the other hand, typical psychic aberrations may result from the stress imposed by the excessive secretion of adrenocortical hormones, as when a tumor of the adrenal cortex causes Cushing s syndrome Thus all bodily functions are closely interrelated and an imbalance of one will surely result in an imbalance of others

STIMULATION OF THE PITUITARY GLAND Since the stress mechanism rests so heavily upon the release of ACTH by the anterior lobe of the pituitary gland and its resulting stimulation of the adrenal cortex, let us examine further the factors which bring about ACTH release

To demonstrate both neural and humoral transmission of impulses to the pituitary, Fortier[9] studied the ACTH response to systemic stimuli (epinephrine, cold and histamine) and to "neurotropic" stimuli (sound, immobilization) The adenohypophysis was separated from the hypothalamic centers in rats through transplantation of the gland of a donor into the anterior chamber of an eye of a recipient, who was later hypophysectomized These animals along with normal controls, were stimulated at weekly intervals and the fall in the circulating eosinophil count was used as an index of ACTH release Epinephrine cold and histamine brought about a definite eosinopenia in both normal and grafted animals Sound and immobilization produced a marked fall in the eosinophil count in the intact but none in the grafted animals It was considered that the data suggested a dual regulation of ACTH release, one purely humoral in response to systemic stimuli, and the other neurohumoral, mediated by the hypothalamic and hypothalamo-hypophyseal neurohumoral pathways In the injured patient the systemic or humoral effects may represent tissue products from the wound as well as epinephrine since though the response is delayed, a metabolic response to amputation in paraplegics does occur

ACTH RELEASE IN NORMAL *VERSUS* STRESSED

SUBJECTS The adrenal cortex evidently has some degree of autonomy independent of stimulation by ACTH, particularly with regard to the zona glomerulosa and its regulation of water and salt metabolism, including the release of aldosterone However, the activity of the adrenal cortex—in the absence of a tumor of this organ, which may or may not be responsive to variations in the plasma level of ACTH—rests largely upon the rate of release of ACTH by the anterior lobe of the pituitary gland *How, then, is the rate of release or production of ACTH regulated in the absence of stress?*

Under normal or nonstress circumstances, it would appear that the rate of release of ACTH is governed by the blood level of adrenocortical corticosteroids (hereinafter referred to as corticoids) It has been shown that in the presence of adrenocortical insufficiency the blood level of ACTH is elevated, and that following an increase in the blood corticoid level produced by giving cortisone the blood level of ACTH is diminished Although the methods available for ACTH measurement require further refinement, it does appear that normally the rate of ACTH liberation into the blood stream for the stimulation of the adrenal cortex is governed in some fashion by the need of the tissues of the body for adrenocortical hormones

In stress, on the other hand, a different set of circumstances exists, and the release of ACTH may be effected by the several modalities previously mentioned

Epinephrine injection can result in a small increase in ACTH release, but the physiologic importance of this phenomenon has been seriously questioned by many

The rôle of nerve impulses can hardly be doubted for Egdahl and Richards[6] stimulated the proximal end of a divided peripheral (femoral) nerve in dogs and produced a rise in corticoid secretion The response to operation in the paraplegic or in patients having spinal anesthesia is delayed, but a delay is not noted when the patient is under general anesthesia where, presumably, nervous impulses can travel immediately from the site of the incision to the brain

THYROID ACTIVITY FOLLOWING OPERATION It has proved exceedingly difficult to demonstrate beyond question that thyroid activity is increased following a stress stimulus.[14] Yet, if increased thyroid activity were to be documented, certain aspects of postoperative nitrogen metabolism might be more readily explained For example, it has long been known that the maximum effect of injected thyroxine is not realized until approximately six or seven days after its administration Since the increased excretion of nitrogen occurs within the first two or three postoperative days, as a rule, it would appear that the effect of thyroxine is not the primary cause of the increased excretion of nitrogen However, more recently *triiodothyronine,* another active thyroid principle, has been available for study; and this hormone, when injected experimentally, produces effects in patients and in animals which occur much more rapidly than do those produced by thyroxine (p 538) The amounts of triiodothyronine circulating in the body are much less than those of thyroxine, but triiodothyronine is far more effective, gram for gram, than thyroxine Therefore, the study of additional thyroid principles may yet reveal that thyroid activity is indeed increased following trauma

The thyroid hormones have multiple effects upon body metabolism, most of which are probably due to the promotion of an increased utilization of oxygen It will be recalled that the patient with thyrotoxicosis has alterations in the nervous system, cardiac irritability, increased cardiac effort, deranged glucose metabolism, liver changes, increased gastrointestinal motility and irritability, and autonomic changes consisting particularly of flushing and excessive sweating

Salt and Water Metabolism in Stress

(1) RENAL EXCRETION OF SODIUM, CHLORIDE, POTASSIUM, AND WATER Immediately following a major operation the urine volume is usu-

ally diminished, there is a retention of sodium and chloride, but potassium excretion is augmented These changes probably represent the net effect of the increased secretion of ADH and of adrenocortical hormones including aldosterone which has been shown to appear in the urine in greater amounts following surgery [78] Cortisone and hydrocortisone may or may not cause a retention of sodium and chloride, depending upon the circumstances but they almost invariably increase the excretion of potassium

BODY FLUID COMPARTMENTS AND PLASMA ELECTROLYTE LEVELS These exhibit fairly consistent alterations following operation The extracellular fluid volume is usually increased at the expense of the intracellular volume and the plasma volume shares in the extracellular increase The plasma sodium level tends to be decreased, though no sodium may have been lost from the body This constitutes a "physiologic" low sodium level The precise cause of this cannot always be explained, but dilution by increased extracellular water often plays a rôle It has not been demonstrated clearly that the sodium content of bone or skin is increased following trauma, to explain a low plasma sodium level.

The volume of sweat secreted is often reduced in the early postoperative period [1] and the sweat electrolyte concentrations vary in the same direction as do those in the urine that is the concentrations of sodium and chloride in sweat (and in saliva) are diminished whereas the concentration of potassium is increased These alterations in both sweat and saliva have been shown to reflect alterations in endocrine and in particular adrenocortical activity Earlier in this chapter it was noted that the volume of gastrointestinal secretions is diminished following major trauma and this too has been correlated with an increase in adrenocortical activity [13]

The practical importance of the diminished urinary output of sodium, chloride and water during the immediate postoperative period is that, since the patient cannot excrete these substances at a normal rate, their administration should be carefully regulated lest circulatory overloading occur The infusion of excessive amounts of non electrolyte-containing solutions may produce water intoxication

Efforts have been made to correlate postoperative intestinal ileus with an increase in adrenocortical activity and with diminished plasma potassium levels, but these studies have not been conclusive That potassium deficiency can result in a degree of paralytic ileus is generally accepted, but it remains to be shown that ileus can result from an increase in adrenocortical activity in the absence of a potassium deficiency

Nitrogen Metabolism

EFFECT OF INJURY. In 1932 Cuthbertson[5] showed that following the fracture of a long bone the excretion of nitrogen and calcium was elevated for a period of many weeks Although such phenomena are now accepted as commonplace at that time these studies occasioned quite a stir in metabolic circles, and they provided one of the pioneer descriptions of the metabolic response to injury Through such investigations it came to be realized that the apparently solid portions of the body were actually masses of constantly moving molecules, as breakdown and repair proceeded continuously and simultaneously Yet not until Schoenheimer and his associates[-4] published their now classic isotopic studies of fatty acid turnover was it realized with crystallizing clarity that virtually all tissue components of the body, including those of bone, are in constant exchange That is the component elements of the various organs are constantly being broken down reused in the metabolic pool, or excreted This concept of the *dynamic state of body constituents* is a basic tenet of modern biochemistry

Since Cuthbertson's report, few other aspects of the stress response have been studied more intensively than has that of nitrogen metabolism (Figs 5 and 6) Lon

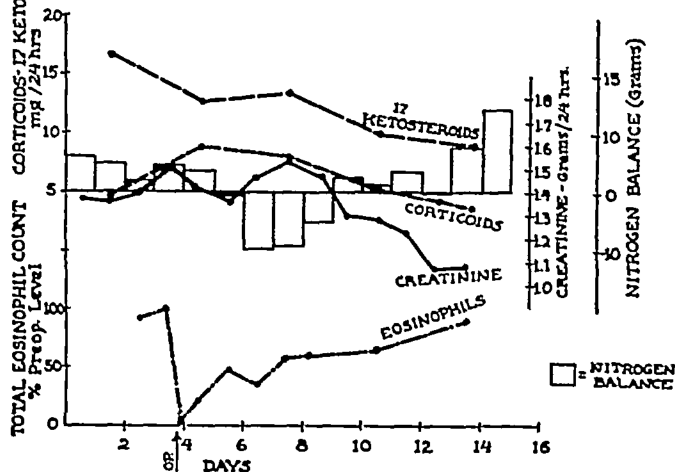


Fig 5 The nitrogen balance was positive prior to operation on the fourth day, and he was retaining several grams daily Following surgery the balance became negative as the nitrogen excretion exceeded the intake The intake of nitrogen and calories remained constant throughout the study The negative balance was greatest on the seventh, eighth, and ninth days, thereafter the nitrogen balance was again positive, and on the fourteenth and fifteenth days (eleventh and twelfth postoperative days) the nitrogen retention exceeded that observed during the control period Of some importance, the alimentation immediately following operation was provided by the intravenous route using protein hydrolysate mixtures—admittedly inferior to the oral ingestion of whole food products (see Fig 30) Nonetheless, this is the usual pattern of nitrogen metabolism seen following trauma The altered adrenocortical activity was reflected in a fall in the total eosinophil count, a rise in urinary corticoid excretion, and a decline in the urinary 17-ketosteroid excretion The metabolic response to soft tissue operations such as colectomy, gastrectomy, or cholecystectomy is not as prolonged as that which follows operations involving bone (Fig 8) (From Hardy, J D, Richardson, E M, and Dohan, C The urinary excretion of corticoids and 17-ketosteroids following major operations correlation with other aspects of metabolism By permission of Surgery, Gynecology and Obstetrics, **96**. 448, 1953)

associates[21] soon found that adrenocortical extract increased nitrogen excretion and liver glycogen formation in the fasted animal, and for some time thereafter it was believed that the increased excretion of nitrogen which followed a major operative procedure was due chiefly to an *increase* in the secretion of adrenocortical hormones However, it was subsequently found by Ingle and his associates[19] and by Engel[8] that the increased excretion of nitrogen following trauma also occurred in the adrenalectomized animal maintained on a constant but adequate supply of adrenocortical replacement therapy This gave rise to the concept that the presence of a certain "permissive" level of cortical hormone is necessary for the nitrogen wastage to occur following injury, but that the increased excretion of nitrogen is not due to the increase in the secretion of the adrenocortical hormones *per se* Recently, it has been suggested that a given amount of cortical hormone may be rendered metabolically more effective during stress—and in view of increasing knowledge that corticosteroid conjugation (inactivation) is a dynamic (and reversible?) process this hypothesis may prove to be a valid one (Fig 11) Meanwhile, there is no doubt that nitrogen excretion is regularly increased by cortical hormone therapy

EFFECT OF ACTH AND CORTISONE ON NITROGEN METABOLISM The increased excretion of nitrogen following the administration of ACTH and/or cortisone has been studied intensively since these substances became readily available The marked losses of nitrogen which accompany the administration of these hormonal agents can be largely compensated for by doubling the caloric and protein content of the diet, though the amount of nitrogen excreted remains considerably elevated over the control levels Furthermore, Sprague and his associates,[27] noting the demonstration by Albright[1] that the negative nitrogen balance of Cushing's syndrome could be altered by the administration of testosterone, found that the negative nitrogen balance produced by 200 mg of cortisone daily was reversed by the administration simultaneously of 25 mg of testosterone propionate Whitney and Bennett[2?] observed that the catabolic effect of ACTH on nitrogen metabolism could be inhibited by a diet high in potassium, and a similar observation was made by Eliel and Pearson[7] in the treatment of a case of Cushing's syn-

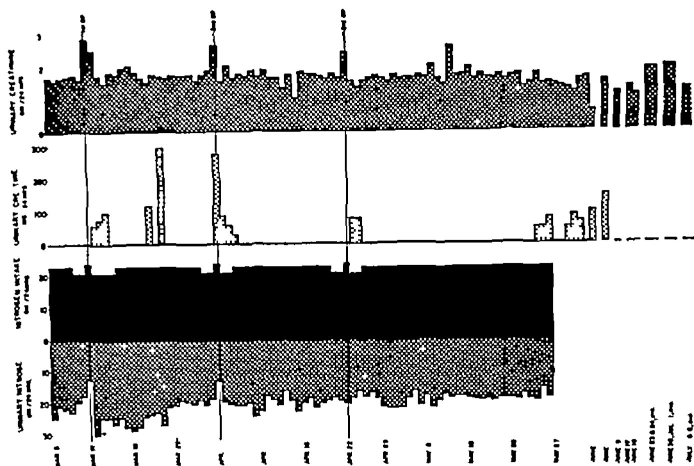


Fig 6 There was an increase in the excretion of creatinine on the day of operation reflecting participation of the muscle mass in the response to the injury The increased excretion of nitrogen following the first operation persisted for almost 12 days, the nitrogenous and caloric intakes being constant throughout. The second and third operations were not followed by nitrogen wastage *This was believed to reflect the fact that after the "mobile nitrogen reserve" has been utilized by a first operation or illness a second insult is not attended by the same degree of nitrogen excretion* (HARDY J D Metabolic reaction to staged operations in man Unpublished data)

drome. Hayes and co workers[15] demonstrated that postoperative nitrogen catabolism could be reduced by the use of androgenic hormones, and subsequent work by others has tended to confirm this

The fact that the usual effects of adrenocortical hormones on nitrogen metabolism and excretion can be altered, if not prevented entirely by the administration of an increased amount of potassium (presumably by preventing the development of a potassium deficit) has been of much interest in the light of reports attesting the importance of *potassium stores in the fabrication* of tissue protein. It has long been known, of course that this element is essential for normal growth and that a deficiency of this cation may cause such pathologic manifestations as weakness or paralysis of various muscles In a series of careful studies, Cannon and his associates[2, 3] showed that adequate *amounts of this ion* are necessary for the synthesis or reconstruction of tissue protein Whereas in protein depleted rats a repletion ration affording an adequate supply of calories, vitamins, amino acids and salts caused excellent acceptance and effective recovery of lost weight, the removal of potassium from the salt mixture in the ration led to poor food consumption, failure to gain weight adequately, development of cardiac lesions characteristic of potassium deficiency and early death. However, the addition of small amounts of potassium chloride

to the deficient ration enabled the animals quickly to achieve effective protein repletion In substance, their investigations demonstrated that a minimal daily intake of potassium salts is required for the processes of protein construction These studies also demonstrated the inability of protein hydrolysate of excellent amino acid composition to produce protein synthesis in the absence of sufficient amounts of potassium Incidentally, commercially available protein hydrolysate solutions commonly contain little potassium

Thus, the question is raised as to whether or not the primary effect of adrenocortical hormones on protein metabolism is not that of the mobilization and excretion of the potassium ion These questions may be answered, in part, through further investigation with recently isolated aldosterone Its metabolic effect is almost entirely upon salt and water metabolism and not upon protein and carbohydrate processes

Finally, the thyroid and the pancreas share in the metabolism of protein materials and, as stated, it is possible that the former plays a large part in the mobilization of nitrogen postoperatively

Carbohydrate Metabolism in Stress

The metabolism of protein was discussed under the general heading of increased adrenocortical activity following trauma because the adrenal cortex apparently has a dominant rôle in the metabolism of this foodstuff The adrenal also has, of course, a part in the metabolism of carbohydrate, but this rôle is not always as clear or definite as is its rôle in protein metabolism It is now desirable to begin a more integrated discussion of the hormonal effects of several endocrine organs in food metabolism For example, it was seen at the close of the discussion of nitrogen excretion above that not only the adrenal cortex but also the thyroid and the pancreas, if not other endocrine organs, are important in the metabolism of protein

Normally one thinks of carbohydrate metabolism as being regulated primarily by the amount of insulin available—inadequate amounts of insulin resulting in inadequate utilization of glucose and excessive amounts of insulin resulting in hypoglycemic shock Nevertheless, insulin does not regulate carbohydrate metabolism without vast assistance from other sources. The intestine is responsible for the adequate absorption of glucose from the ingested foods Hypoglycemia may be a cause of death in the presence of inadequate liver function, for, to maintain a constant and uniform supply of glucose fuel it is necessary to store glycogen in the liver and, perhaps to a lesser extent, in the muscles Accordingly, abnormalities of glucose metabolism are common in liver failure. Furthermore, glycosuria and hyperglycemia are often found in the presence of adrenocortical hyperfunction, such as occurs with ACTH and/or cortisone therapy, or in the presence of Cushing's syndrome. In Addison's disease or hypopituitarism, on the other hand, hypoglycemia may be a cause of death Finally, to give one more example of endocrinologic alteration in glucose metabolism, patients with thyrotoxicosis may exhibit glycosuria and hyperglycemia

Thus, the regulation of the normal blood sugar level represents the net effect of a delicate balance of a considerable number of factors

"STRESS DIABETES" Usually the rise in the glucose level following stress is not great, but in severe and prolonged stress this level may increase from the normal of approximately 100 mg per 100 cc of blood to from 400 to 700 mg This has often been observed following extensive trauma, including burns, and during the past several years we have observed it in two other diseases The first patient was an individual who had had a recurrently infected lung cyst for a number of years, during which time he had gradually developed diabetes mellitus for which he was eventually receiving more than 100 units of insulin daily, in combination with a rigid diet To facilitate control of the diabetes by

abolishing the intermittent infection in the lung the cyst was resected To the surprise of all within the next few weeks the diabetes improved to the extent that the insulin was stopped entirely and, eventually very little dietary restriction was necessary This was interpreted as evidence that the stress of chronic sepsis had increased the insulin requirements, presumably by increasing factors antagonistic to insulin (adrenocortical hormones?) To our knowledge decreased insulin production in stress has not been demonstrated

The second patient was a woman who had had an operation for atelectasis of a portion of the right lung (due to a bronchial adenoma it was later shown) The bleeding encountered had been such that the operation was abandoned but apparently a bronchus had been entered in the dissection and postoperatively she developed a bronchopleural fistula and empyema This was drained and over the next 8 to 10 months she had a bronchopleural cutaneous fistula She sustained great weight loss and developed diabetes mellitus for which she eventually received insulin At the time of her admission to the University Hospital the diabetes was discovered and was brought under control prior to operation The bronchograms demonstrated extensive destruction of the right lung due to infection distal to an adenoma which now occluded the right main bronchus and a pneumonectomy was performed Following the pneumonectomy a staged thoracoplasty was carried out to close the residual space As convalescence progressed and the sepsis cleared the blood sugar level declined to normal without insulin In other words, the diabetes had apparently been cured by removal of the chronic stress of sepsis, and similar experiences have been reported by others.[10] Therefore again it must be remembered that insulin and cortical hormones are physiologic antagonists The diabetes of total pancreatectomy is ameliorated by adrenalectomy and the hypoglycemia associated with functioning hepatic metastases of a tumor of the Isles of Langerhans has been effectively combated by the administration of cortisone This hormone will maintain an adequate blood sugar level in patients with Addison s disease in the presence of prolonged fasting. Again, further clarification of these relationships awaits a suitable method for the measurement of blood insulin levels

THE NITROGEN SPARING RÔLE OF CARBOHYDRATE. The foregoing discussion of carbohydrate metabolism has not included the interrelationships which have long been known to exist between the availability of calories in the form of carbohydrate and fat on the one hand, and tissue protein catabolism on the other

Metabolism of Lipids in Stress

Until relatively recently the metabolism of lipids in stress was less extensively studied than was that of protein and carbohydrate and indeed there was the impression that fat shared little in the response to operation The work of Moore and his associates,[23] however has indicated that considerable amounts of fat are burned as fuel in the immediate postoperative period These conclusions were based upon both total body water determinations and the measurement of the respiratory quotient in postoperative patients The adrenocortical hormones will probably be found to have an important rôle in fat mobilization In fact, there is considerable evidence to indicate that adrenocortical hormones can and do have a rôle in fat metabolism For example, the abnormal distribution of fat in patients with Cushing s syndrome is well known, and recent studies in adrenocortical hyperplasia have shown that when the excessive androgen production (which causes the adrenogenital syndrome) is suppressed by the administration of cortisone, there may occur such a rapid redistribution and deposition of fat as to cause white striae of the skin beneath the female contours which develop This redistribution of fat in the female is due to the interrelationships which exist be-

tween the adrenocortical hormones and the secretion of estrogens, and considerable research is now being devoted to the rôle of androgens and estrogens in the metabolism of proteins and fats Obviously these hormones are important in protein anabolism the female who has excess androgen production exhibits increased muscular development

The metabolism of lipids is considered further under nutrition

Miscellaneous Further Comment on the Stress Response

BODY TEMPERATURE. A mild increase in body temperature, at times following an initial decrease immediately after the trauma, is a part of the alarm response (Fig 7) Patients who have a clean herniorrhaphy with no "foreign body" reaction or infection almost always exhibit some mild rise in temperature during the first few days following operation Moreover, the rise in temperature is somewhat proportional to the degree of the trauma However, when major trauma has occurred it is often impossible to exclude the possibility that infection or the absorption of blood or damaged tissue may not be responsible for the febrile response As noted above, studies which we conducted some years ago indicated that patients sweated with less facility postoperatively than they did preoperatively,[12, 14] and it appeared that postoperative fever might be due in part to a diminished rate of heat loss, regardless of whether actual heat production was increased (p 369)

If there is a useful purpose in such fever following trauma, it would appear to reside in the fact that the rate of almost all chemical reactions is increased by an increase in temperature and, in the last analysis, the stress response consists of myriad individual chemical reactions Moreover, evidence indicates that the stress response results not from a different chemical reaction but from alterations in the rate of chemical reactions which occur normally

MUSCLE PARTICIPATION IN STRESS RESPONSE It would be surprising indeed if the musculature did not participate in the stress response, and of course it does Alterations occur in the water and electrolyte content of muscle cells, and in muscle's rôle in carbohydrate metabolism Moreover, urinary creatinine excretion is frequently increased following trauma, and the rate of creatinine excretion in health is usually considered an approximate index of the rate and magnitude of muscle metabolism In wasting diseases, the urinary excretion of creatinine gradually declines as the muscle mass shrinks, as the lean tissue is reconstituted during convalescence, the daily creatinine

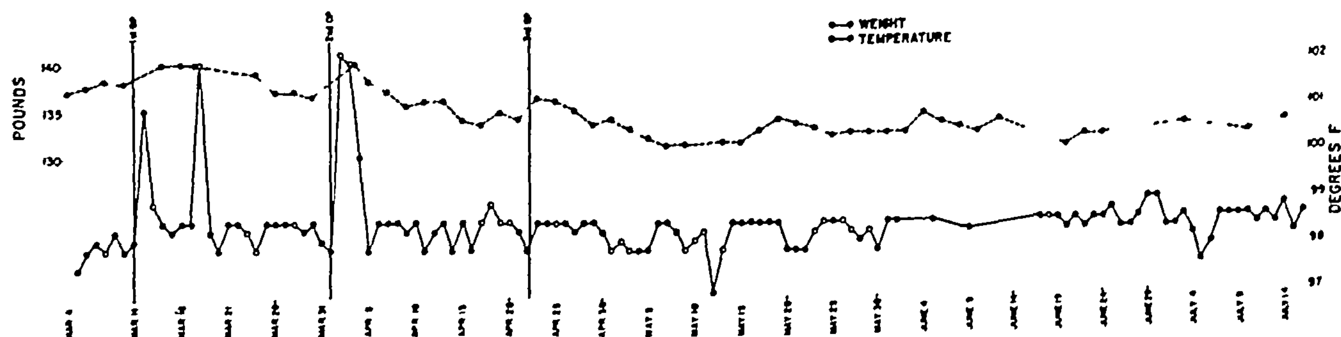


Fig 7 The body temperature rose after each of the first two operations but not after the third Most operations are followed by a "stress" febrile response of various magnitudes The body weight curve rose slightly after each operation due to retention of fluid in which nitrogen and calories were given intravenously, but the over-all trend of the weight curve was downward over the period embraced by the three stages Most patients lose 10 lb or more (4.5 kg ±) following a major operation This loss consists of both fat and lean tissue During convalescence the lean tissue tends to be regained first, then fat (HARDY, J D Metabolic reaction to staged operations in man Unpublished data)

excretion gradually returns to the preoperative level Fever and hyperthyroidism also increase creatinine excretion.

THE RÔLE OF ENZYMES IN STRESS A discussion of the systemic reaction to injury should not be concluded without at least mention of the rôle of enzymes, for there is increasing evidence that the ultimate chemical reactions which in the aggregate constitute the response to trauma are regulated by enzyme systems which are in turn influenced by hormones The status of enzymes in modern surgical physiology will be discussed later in a separate chapter, but it may be noted here that it will doubtless be demonstrated that many of the phenomena of stress which we now must accept as being due to altered endocrine activity" will ultimately be traced to specific enzymic changes (Fig 71)

The Metabolic Response to Injury: Recapitulation

A traumatic injury initiates a series of metabolic forces which constitute at once the catabolic reaction to the immediate insult and also the positive forces which will develop and motivate the repair itself The processes of recovery from the insult are collectively termed *convalescence* It has been seen that all systems of the body respond to severe trauma, doubtless with the purpose, if at times obscure, of permitting the individual to survive the episode The length of time that the acute forces are in action will depend upon the magnitude of the operation in the physiologic sense, since it appears that operations which involve bone produce more prolonged metabolic changes than do those which involve only soft tissue as, for example cholecystectomy and gastric resection Moreover, since there is such a marked variation in the response to different operations we have chosen to compare common metabolic alterations in graphic form It will be seen in Figures 6 and 8 that the response to a thoracoplasty is more prolonged than the relatively brief response to gastric resection (Fig 5) The response to an extensive thermal burn (Fig 51) exceeds the response to any operation that we have studied

The "feed back" mechanisms which arise to reverse the metabolic response to surgery, once it has served its purpose, are largely unknown

The Stages of Convalescence

It remains to correlate the various facets of the response to operation—the psyche, the wound and the general metabolic response Moore[23] has offered a clinical correlation which we feel is particularly well developed and which is useful in better visualizing the complex physiologic phenomena that constitute convalescence. He divided convalescence into four stages the *adrenergic-corticoid phase*, the *corticoid withdrawal phase*, the *spontaneous anabolic phase*, and the *fat gain phase* Of course, there is overlapping between these various stages, but it does afford a framework within which one can correlate observed clinical findings with the metabolic changes which are defined by laboratory study Again, it is the injury itself which activates the forces of convalescence, this having been recognized by John Hunter two centuries ago Moore's paper has been drawn upon liberally in presenting the following outline but modifications have been made

Phase 1: The Adrenergic-Corticoid Phase

CLINICAL The patient goes to the operating room, anesthesia is induced the operation is performed, and convalescence begins The first clinical findings of note are those caused by adrenal medullary activity an increase in pulse rate a narrowing of the pulse pressure peripheral vasoconstriction with or without sweating, and an elevation of the blood sugar level due to glycogenolysis These changes may occur with apprehension alone or during the excitement stage of ether anesthesia, subsiding as the patient is lowered into deeper anesthesia and stabilization of the respiratory and circulatory functions is achieved. Spinal anesthesia, intravenous barbiturates, and drugs which in-

G.Q.(♂): EFFECT OF THREE-STAGE THORACOPLASTY ON THE EOSINOPHIL COUNT AND URINARY EXCRETION OF CORTICOIDS AND 17-KETOSTEROIDS

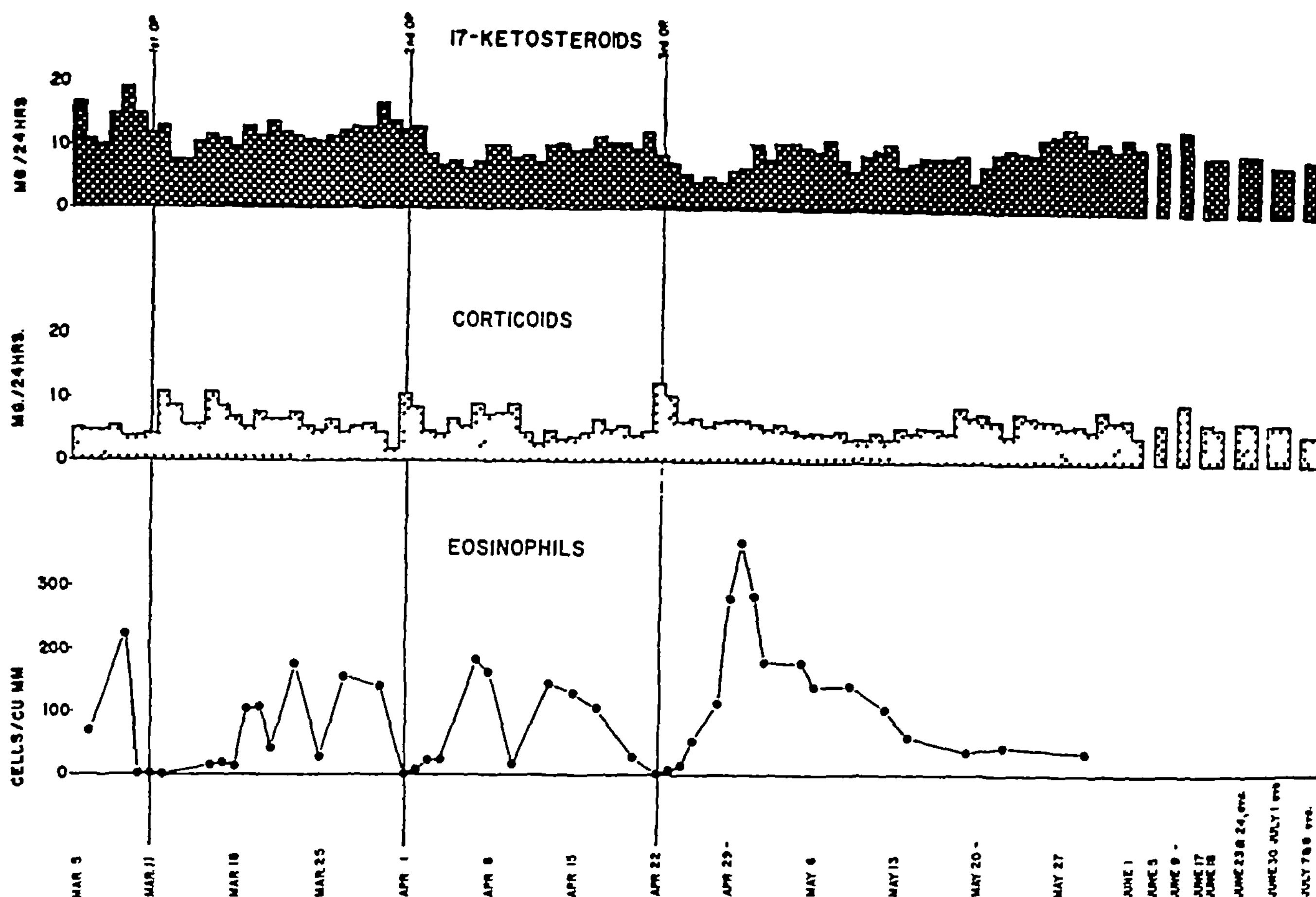


Fig 8 The excretion of 17-ketosteroids showed an immediate fall after each operation, and a gradual general decline over the period embraced by the three stages The level of this excretion provides one index of the general state of health, declining during prolonged illness and rising again to normal during convalescence The excretion of corticoids was increased after each operation, reflecting a continued capacity to respond to repeated trauma The total eosinophil count fell to zero following each "stage," and gradually rose thereafter, the "rebound" to supernormal levels following the third stage was particularly noteworthy (HARDY, J D Metabolic reaction to staged operations in man Unpublished data)

terfere with normal autonomic transmission result in alteration of the adrenal medullary phase, either decreasing its intensity or delaying it Actually, the most intense type of adrenal medullary response is observed in trauma in the unanesthetized individual, a common example being the wounded soldier or the traumatic injury in civilian practice

Within a few hours the patient emerges from the anesthesia and complains of incisional pain He is listless and the preoperative excitement and apprehension have disappeared Peristalsis is quiet and will probably be absent for the next day or so The pulse rate may continue rapid for approximately 24 hours and rectal temperatures will demonstrate an elevation in the body temperature (Incidentally, a common nursing omission is the failure to take all temperatures rectally in patients who have *nasogastric suction or who may be taking* sips of water, here the oral temperature may not reflect the actual body temperature) There is a relative oliguria the day of operation unless excessive amounts of water have been given, but during the following days the urine output will rise

Thus, during the adrenergic-corticoid phase the patient has little interest in his surroundings The end of this phase is defined by the beginning of peristalsis, the passage of flatus, the return of a degree of appetite, and an increasing interest in the environment

THE WOUND. During the adrenergic corticoid phase the strength of the wound is dependent almost entirely upon the sutures If it is necessary to open the wound to evacuate a hematoma, it falls apart quite easily on simply spreading with a hemostat Fibrin clot and matrix has sealed the edges of the wound, but there is no particular healing from fibroblastic activity The usual local cellular picture of inflammation is present, and there arise forces in the injured cell loci to cause regrowth of these cells until existing tissue gaps are filled Moreover, humoral factors from the wound itself influence general metabolism

METABOLIC There is a decrease in body weight (Fig 7) due in part, not only to the catabolism of lean tissue with nitrogen loss in the urine but also to the utilization of body fat The characteristic nitrogen loss has been described in some detail This increase in nitrogen excretion in our experience begins in earnest on the second postoperative day and continues for a variable number of days depending upon the magnitude of the operation (Figs 5 and 6) Potassium excretion is increased and sodium excretion is diminished The caloric intake of the individual is usually reduced during the immediate postoperative period and this, in itself has been shown to be a potent stress stimulus for many of the metabolic activities previously regarded as entirely due to the operation furthermore the untoward effects of operation may be diminished by giving the patient an adequate caloric intake during this period However the writer, for one, while making every effort in the past to achieve alimentation in the early postoperative period has never been convinced that any particularly useful function is achieved by forcing food upon patients at this time

The *total eosinophil count falls* during the adrenergic-corticoid phase to or almost to, zero then it gradually rises during the next few days In general it is fairly well correlated with the increase in the urinary excretion of corticoids (Figs 8 and 9), though this correlation is by no means an exact one, and actually a cause and effect relationship should be advanced with some caution In other words, the factors which produce an increase in the corticoid secretion in trauma may also cause a decrease in the total eosinophil count—this despite the well-known fact that the administration of ACTH and/or cortisone will usually cause a fall in the total eosinophil count

The *hydrocortisone secretion per minute* has been measured during operation by collecting left adrenal vein blood at laparotomy (Figs 10 and 11) The level of free hydrocortisone in adrenal vein blood was 224 gamma per cent, compared with 24 gamma per cent in peripheral blood

During this first phase the plasma sodium level may be diminished and the bicarbonate level increased The total body water volume changes only slightly, despite weight loss This fact has been interpreted, with supporting data, to indicate that a considerable amount of body fat is burned for fuel during this acute injury phase

The end of Phase 1 is signified by the return of the eosinophils to a high level and the lowering of urinary nitrogen excretion, along with the clinical findings which have been mentioned

Phase 2: The Corticoid Withdrawal Phase

CLINICAL. This phase of normal convalescence begins about the fourth day and lasts from two to three days after extensive surgery such as a gastric resection occupying the period from about the fifth to the seventh or eighth day The appetite has improved considerably and peristalsis has increased spontaneous physical activity is rapidly increasing and the usual interest in surroundings and visitors has returned Moore makes the point that during this period the patient's interest in activity is frequently greater than his ability to follow through characterized by the fact that while the patient is most anxious to get a newspaper he can read but a few paragraphs before he lies back and lays the paper down.

Phase 2 is also the time when *water diu*

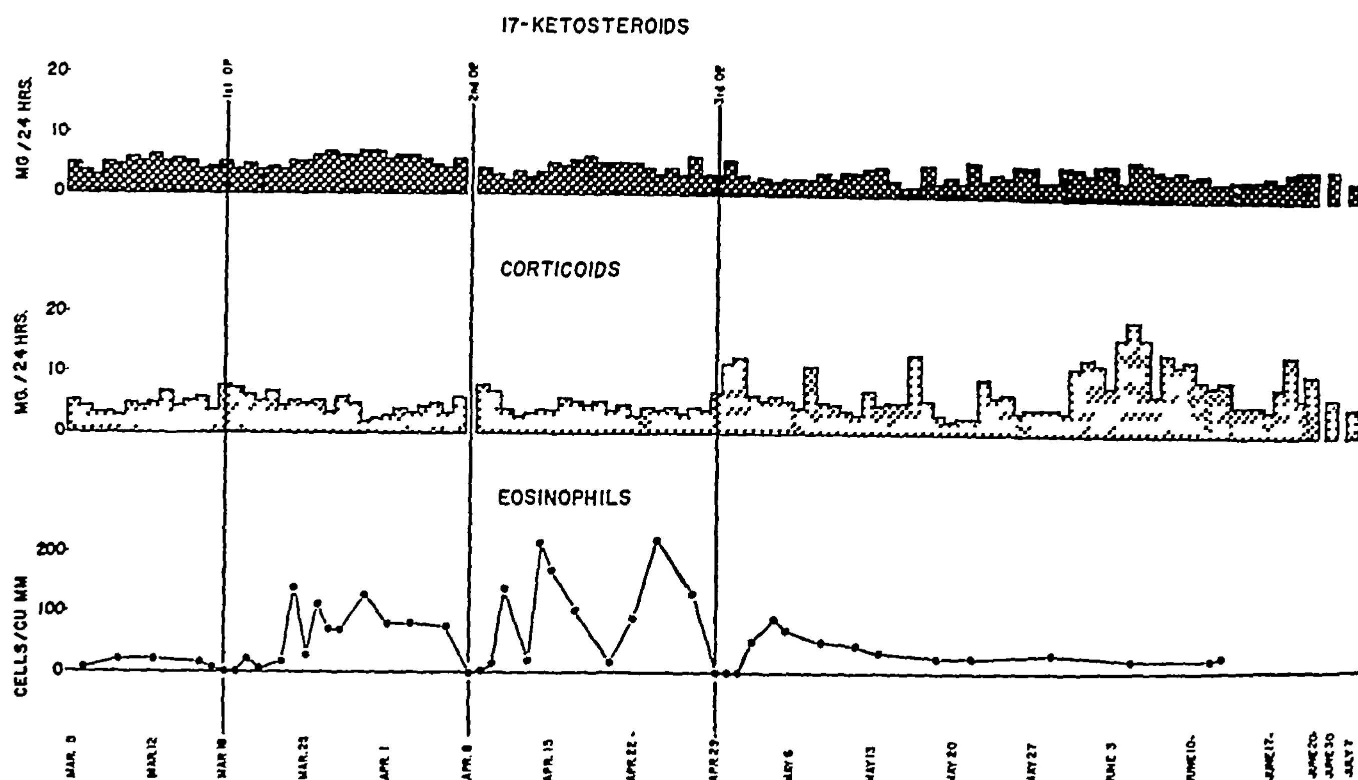


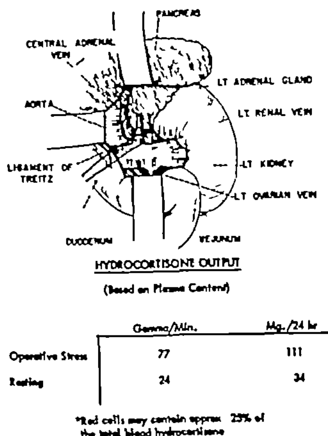
Fig 9 The chronically and severely ill individual presents characteristic patterns of urinary steroid excretion and of other metabolic responses to surgery Note the low level of 17-ketosteroid excretion throughout the entire 4-month period of the study (average normal for adult males, 15 mg per 24 hours—in our laboratory) The level of corticoid excretion was little affected by the first two operations The chronic stress was further reflected by the low control total eosinophil counts, the very mild postoperative rebound phenomena observed after all operations, and the prompt return to the low control level following the third operation (From Hardy, J D *Surgical Physiology of the Adrenal Cortex* Springfield, Ill , Charles C Thomas, 1955)

resis occurs, probably due to the interaction of the decline in the previously increased secretion of adrenocortical hormones and, probably also, to a diminished secretion of the posterior pituitary antidiuretic hormone Actually, the diuresis may exceed what is necessary or "overshoot " The weight curve (Fig 7), after rising due to the retention of fluid infused postoperatively, may briefly fall below that which is seen on subsequent days

THE WOUND During the second phase the wound has become painless unless suddenly subjected to tension or unless infection is threatening, and microscopic study during this period shows that there is marked fibroblastic proliferation The tensile strength of the wound is rapidly increasing (*see* wound healing curve, Fig 37) and by the sixth to the eighth day epithelization has occurred to the extent that the skin sutures have usually been removed from an abdominal incision To drain such a wound, more than a blunt instrument such as a hemostat is needed, and the line of incision has become red

METABOLIC Changes during the second stage are in many respects a continuation of those occurring during Phase 1, but there is less evidence of fat combustion and there is a better correlation between water excretion and nitrogen metabolism, particularly as regards weight loss Positive nitrogen balance is rapidly being achieved, due both to the diminished effect of the initial trauma and also to the fact that the oral intake of nutritional substances has been increased

The potassium excretion in the urine is diminishing, whereas that of sodium is in-



	Gamma/Min.	Mg./24 hr
Operative Stress	77	111
Resting	24	34

*Red cells may contain approx. 25% of the total blood hydrocortisone

Fig 10 Direct measurement of hydrocortisone secretion *Above* Left adrenal gland as exposed at laparotomy By aspirating only adrenal vein blood (renal vein blood temporarily excluded by loop of silk) over a timed interval the steroid secretion per minute was measured *Below* Hydrocortisone secretion in man as determined by left adrenal vein blood samples Since hydrocortisone represents 85 per cent of the corticoid secretion in man, the measurement of hydrocortisone output reflects with considerable accuracy the level of adrenocortical activity The values given represent only approximations, especially in the case of the "resting values Yet the data obtained by this direct method agree remarkably well with those reported by previous workers using indirect methods (From Hardy J D Turner, M D, Ward V, and Carter T Steroid metabolism in man Surgery 42: 194 1957)

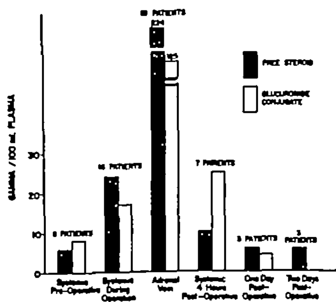


Fig 11 During operation the plasma level of free (active) hydrocortisone was 23 μg per 100 cc in peripheral vein blood and 221 μg per 100 cc in adrenal vein blood Since the adrenal cortex supposedly secretes the active hydrocortisone in the form of the free alcohol the relatively high level of conjugated hydrocortisone in adrenal vein blood is not readily explained for this level far exceeds that of the entering arterial blood It has been shown that to a degree extrahepatic conjugation (inactivation) can occur in the circulating blood but that following hepatectomy the capacity of an animal to conjugate hydrocortisone is lost in 6 hours The very high level of free hydrocortisone in adrenal vein blood may have facilitated more rapid conjugation in plasma The disproportionately high level of conjugated hydrocortisone in systemic blood 4 hours after operation presumably reflected inactivation of the large amounts of the free steroid secreted during stress by the following day the control levels of both free and conjugated hydrocortisone had been regained. (From Hardy J D Turner, M D Ward V and Carter, T Steroid metabolism in man Surgery 42: 194 1957)

creasing. The eosinophil count has risen to normal or above normal limits (Fig 5) and the urinary corticoid excretion has subsided to control levels or to levels slightly below those recorded during the control period Perhaps this decline in corticoid excretion to levels below those present preoperatively has the physiologic purpose of allowing normal metabolic rates and activities to reestablish themselves. The sodium level of plasma is returning to normal despite an increased sodium excretion in the urine

The end of Phase 2 is signaled by the return of the various indices of the acute stress response to preoperative levels and the availability of sufficient nutritional intake to permit this return

Phase 3: Spontaneous Anabolic Phase

CLINICAL. This phase is initiated when adequate calories and other nutritional sub-

stances are provided After major abdominal injury Phase 3 begins on from the seventh to the tenth postoperative day During this time the patient's strength and appetite have increased *pari passu* with his activity, and he is beginning to be anxious to be discharged "The telephone is in frequent activity and visitors are welcomed and urged to remain longer An intense interest in business requirements is developed, and it is realized that time has been lost from the usual occupations "[23] The plasma chemistry measurements are not remarkable, and to measure the metabolic activity which is proceeding, one must perform metabolic balance studies and total body water measurements to demonstrate that during this period lean tissue is being reconstructed, body fat is being deposited, and stores of other substances lost during the acute injury are being replenished

THE WOUND Now the wound is returning rapidly to normal tensile strength and should not give pain If it does, one should look for the presence of infection, perhaps previously suppressed by the administration of antibiotics Some induration and overgrowth of the tissue elements producing the wound healing are notable and the incision is still a dull red However, the biologic forces ("wound hormones"? enzymes?) which produced cellular repair of the wound, even excessive repair, are now giving way to the local (?) forces which inhibit further proliferation The cellular inflammatory reaction which resulted in repair subsides

METABOLIC The *body weight curve* is beginning to turn upward, following the decline during the first two phases of convalescence, furthermore, there is a good correlation with nitrogen retention during this period, indicating that fat gain is not prominent The provision of more than the optimal caloric intake during this period does not further increase the nitrogen retention in most patients

During this phase some potassium is being regained (positive balance) A zero sodium balance is present, indicating neither excretion nor retention of this ion, the output being equal to the intake The rebound phenomenon in the total eosinophil count (Fig 8) has subsided, and the level is flattening toward control levels, as is the excretion of corticoids During the late anabolic phase the level of excretion of 17-ketosteroids begins to rise toward normal, following the postoperative decline However, after a severe debilitating injury the normal excretion of 17-ketosteroids is not regained for many weeks There is some increase in total body water during the third phase, due to the fact that lean tissue contains approximately 73 per cent water (Fig 13)

Phase 4: The Fat Gain Phase

Clinically, the patient has gone home and gradually resumed his usual activities Weight gain is prominent and this weight is chiefly due to lean tissue but, as the lean tissue reserves are restored following the losses in nitrogenous substance after injury, the fat gain period begins If the diet is plentiful and the physical exertion not excessive, there is a fairly rapid restoration of body fat which begins during the third or fourth week following operation and lasts for many months Moore emphasizes that the most outstanding clinical phenomena in the fat gain phase are a gain in body weight and a return of normal sexual activity Of course, if the operation has interfered with normal gastrointestinal function, such as a nearly total gastric resection, the patient may not gain weight and may actually continue to lose weight until a very lean level has been reached

During the fourth phase the wound flattens out The scar broadens somewhat and turns white, however, gradual alterations in its appearance and character may continue for months Nitrogen, potassium, sodium, eosinophil counts and steroid excretion are within normal limits The excretion of 17-ketosteroids gradually increases with the return of health, and it has been suggested that this excretion is useful as an index of the rate and progress of convalescence

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Chapter 2

Body Constituents: Water and Solids

Body composition, acid-base regulation, hormonal factors in body fluid metabolism, renal function, daily water balance, types of fluid imbalance, a general approach to fluid therapy, and specific pathologic fluid states in surgery are the topics that will be considered in this chapter

Introduction It is no longer permissible to consider extracellular fluid as functionally separate from intracellular fluid Nor is it realistic to discuss body water without acknowledging the dynamic molecular interchange between body water and body solids Hydrogen and oxygen, for example, are continuously being incorporated into metabolic compounds, and simultaneously these atoms are being freed from other organic compounds to form water Therefore, while in the ensuing pages we shall for convenience discuss body water apart from body solids, the reader must remain constantly aware that the skin of a human being encompasses a mass of watery tissue the elements of which are in rapid turnover this total body mass must be conceived of as representing a single functional unit *This concept of the functional unity of body constituents represents the very essence of modern physiology*

Body Composition

Methods of Measuring Body Water and Solids

Early measurements of body content of water and solids were achieved by desiccation procedures, and one of the first studies reported in man was that of Bischoff[6] in 1863, he estimated the body water content of a cadaver at 58 5 per cent of body weight In 1941 Behnke[4] showed that in normal subjects the determination of body specific gravity enabled one to estimate the body fat content Fat, with its low specific gravity of 0 92, was identified as the primary variable that determined body density in health, and upon the basis of these studies Behnke formulated the now widely used concept of the *lean body mass* He pointed out that the body consists of a fat free portion of essentially constant gross composition and of a variable quantity of fat It was later demonstrated that if the body weight and the body fat content of a normal subject are known, then the body water can be calculated—for body water and body fat bear an inverse relationship to each other, the greater the percentage of body weight represented by fat the less the percentage represented by water

DILUTION METHOD (FIG 12) Useful as were the data derived from desiccation and specific gravity studies, these procedures were of course not applicable to the routine study of normal and ill human beings There remained the need for some method of measurement which could be readily applied in living persons in the clinic A variety of substances were tried but of these only urea, aminopyrine, and heavy water have enjoyed widespread usage Of these three, heavy water (deuterium oxide, D_2O) has achieved importance since von Hevesy and Hofer[27] advanced it for this purpose in 1934 It has

been found to be well tolerated by the organism, it equilibrates rapidly (1 to 2 hours) with body water in normal subjects, it is not selectively stored or excreted, and it is not metabolized to any significant extent While the technics are laborious, the concentration of deuterium in urine and plasma can be accurately measured by certain physical methods, the most commonly used ones employing either the mass spectrograph or the falling drop apparatus Aminopyrine, while to an extent metabolized in the body, is much more readily measured in body fluids and thus it is being increasingly used in clinical studies

Total Body Water and the Body Fluid Compartments

To examine specifically the range of percentage body water in persons of different habitus we used D_2O to study a group of healthy adult male and female subjects ranging in size from the very lean to the very obese (Fig. 13) The leanest male subject had a total body water value of 71 per cent of body weight (44 5 L), and the most obese male subject had a total body water value of 42 per cent (48.3 L)[23, 46] Similarly, the leanest female subject had a total body water value of 68 per cent and the most obese female subject a body water value of 50 per cent In general the values for percentage of body water of female subjects appeared to be somewhat lower than those for male subjects of corresponding weight and habitus The average value for body water for eight healthy men was 60 per cent of body weight, and the subjects who individually had values in the immediate range of 60 per cent were merely of good nutrition being neither skinny nor fat. Comparable values were obtained by Schloerb and his associates,[49] who found that the average healthy young adult male contained 61 8 per cent water and the young adult female 51 9 per cent

Thus it has become necessary to revise previous concepts concerning the average percentage value for body water content in healthy adults, the previously used figure of 70 per cent being acceptable only in the unusually lean subject It is hazardous to calculate fluid replacement and drug dosages solely on a weight basis in the very obese, for fat is *relatively* inactive metabolically Hence, the use of some convention such as "ideal" body weight for the average person would appear to have real merit where the estimation of drug dosages is concerned Finally the fact that women tend to lose less nitrogen than men following a given operation[23] may merely reflect the presence of less lean tissue to give up nitrogen

BODY WATER IN DISEASE STATES A moment's reflection will render it obvious that the percentage of body weight represented by water will vary markedly in different disease states For example the dehydrated

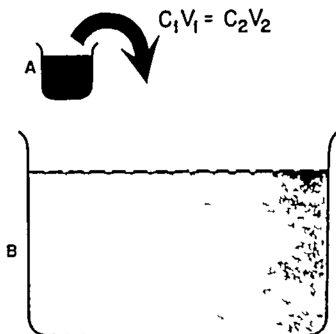


Fig 12 All dilution methods for measuring volumes are based on the principle that when the concentration (C_1) and the volume (V_1) injected as well as the subsequent concentration in plasma following equilibration (C_2) are known—that is when three of the four members of the formula are known—then the fourth (V_2) can be solved for The same relationship applies whether the concentrations are determined by measuring color change (as with T 1824) density (as with heavy water) or radioactivity (as with radiosodium)

TOTAL BODY WATER (D_2O DILUTION SPACE) AND BODY SIZE RELATIONSHIP

Subject	Mass, W	Stem length, L	Nutritive Index, N_o*	N_o-N_m†	Percentage overnutrition above minimum value, $\left[\left(\frac{N_o-N_m}{N_m}\right) \times 100\right]$	Total body water: Amount	Per cent of body weight	Per cent deviation from maximum value
	kg.	cm.			Per cent	l.	Per cent	Per cent
Leanest (theory)	(56.4)	(91.0)	(0.42)†	(0.00)	(0.0)		(75)	(0.0)
J.M. ♂	60.9	91.0	0.43	0.01	2.4	44.5	73	2.4
H.G.B. ♂	60.0	81.3	0.48	0.06	14.3	41.1	69	8.0
J.D.H. ♂	77.3	83.8	0.51	0.09	21.4	46.6	61	18.7
J.R. ♂	66.4	76.0	0.53	0.11	26.2	37.6	57	24.0
W.B. ♂	121.0	90.2	0.55	0.13	31.0	60.6	50	33.4
S.G. ♂	116.0	81.5	0.60	0.18	42.9	48.3	42	44.0
M.McG. ♀	53.7	90.2	0.42	0.00	0.0	36.4	68	9.3
A.D. ♀	59.1	82.6	0.47	0.05	11.9	35.3	60	20.0
J.R. ♀	54.6	75.0	0.51	0.09	21.4	31.7	58	22.7
W.T. ♀	86.4	76.2	0.58	0.16	38.1	45.1	52	30.6
Fattest (theory)	(111.0)	(76.2)	(0.63)	(0.21)	(50.0)		(40)	(46.7)

* N_o = observed nutritive index = $W^{1/3}$ gm./L cm. (Cowgill and Drabkin, 1927)

† N_m = minimum nutritive index, or minimum value of N_o = 0.42

Fig 18 Total body water (D_2O dilution space) and body size relationship These healthy individuals were selected to cover a wide range in degrees of obesity The leanest male (J M) had a body water of 44.5 L which represented 73 per cent of body weight (60 9 kg), the most obese male (S G) had a body water of 48 3 L which represented 42 per cent of body weight (116 0 kg) Subject J M contained only 2 4 per cent fat in excess of the minimum normal value, whereas subject S G contained 42 9 per cent fat in excess of the minimum normal value Similarly, in subject J M the value for body water (44.5 L) was only 2 4 per cent less than the theoretical maximum normal value, whereas in subject S G the value for body water (48.3 L) was approximately 44 per cent less than the theoretical maximum value (75 per cent of 116 0 kg) These data show that if in normal persons the total body water is measured, the body fat can be calculated and *vice versa* Moreover, by substituting in the formula of Cowgill and Drabkin the values for weight and stem length, a useful approximation of the body fat (and water) content can be achieved in normal subjects (From HARDY, J D , AND DRABKIN, D L In *Fluid Therapy,* by Hardy, J D Philadelphia, Lea & Febiger, 1954)

individual will exhibit not only an absolute reduction in body water content, in liters, but he will also exhibit a diminished proportion of body weight represented by body water, that is, body water would be reduced whereas body solids and body fat might not be proportionately reduced over a short period of time On the other hand, the patient with cardiac decompensation, or one who has abnormal deposits of fluid from other causes, may contain considerably more than 70 per cent body water For example, one patient we studied during an episode of cardiac decompensation had a value of 83 per cent before his edema fluid had been mobilized with digitalis therapy and mercurial diuretics

The Body Water Compartments

THE INTRACELLULAR COMPARTMENT It has been customary to view the total body water as being contained in two major compart-

ments—the *intracellular* and the *extracellular*, the latter being further divided into the *interstitial* water and the *plasma* water. The intracellular water is measured by subtracting the value obtained by the measurement of extracellular water from the total body water (measured with deuterium oxide, antipyrine, urea, or other substance). These relationships are shown in Figure 14. In health the intracellular water represents approximately two thirds or from 65 to 70 per cent of the total body water. It will be clear that the estimation of intracellular water rests entirely upon the validity of the measurements of extracellular water and total body water since, as noted above, the value for intracellular fluid is obtained by subtracting measured extracellular fluid from measured total body water. Unfortunately, there still exists considerable controversy regarding the accuracy of the various technics utilized for the measurement of extracellular water.

EXTRACELLULAR WATER. As with total body water, numerous substances have been employed for the measurement of extracellular fluid utilizing the dilution principle. Of these only sodium thiocyanate and inulin have had wide usage. In general the measurements of extracellular volume in lean subjects have usually resulted in values representing approximately 22 per cent of actual body weight and 32 per cent of total body water. Measurements with inulin, which is perhaps most generally accepted as the more reliable substance for this purpose, have resulted in values for the extracellular fluid in the neighborhood of 15 per cent of body weight. Thus values for extracellular water obtained through measurement with inulin are lower than those obtained with thiocyanate. There is no doubt that thiocyanate does enter some cells and a correction is usually made for that which enters red cells. Moreover, in certain disease states the thiocyanate volume of distribution increases considerably. Ariel and associates[3] demonstrated a marked

BODY COMPOSITION OF A NORMAL MALE OF AVERAGE OBESITY

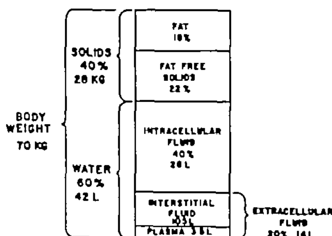


Fig. 14. During illness the relative proportion and absolute mass of any of the several body components may change. Water is gained in heart failure and lost in vomiting. Fat is gained in health and lost in illness. In Cushing's syndrome there exists the unusual circumstance of fat gain with lean tissue loss. Usually, however, both fat and lean tissue are lost together during illness and regained during convalescence—though the timing of the losses or the gains of these two tissues may be different (see text). (From HARDY, J. D.: *Fluid Therapy.* Philadelphia, Lea & Febiger, 1954.)

increase in patients with a perforated peptic ulcer.

For practical purposes, the extracellular fluid represents approximately one-third, and the intracellular fluid two thirds, of the total body water. It has been shown that both volumes are more closely related to total body water than to body weight, and that each is inversely related to body fat. In the healthy person weighing approximately 70 kg. and containing 42 L. of water, the intracellular fluid would represent approximately 28 L. of water and the extracellular water approximately 14 L. of water (Fig. 14). *The visible clinical signs of body water loss are due largely to deficits in the extracellular fluid volume,* and it is helpful in clinical therapy to have some value in mind regarding the volume of water by which the extracellular fluid compartment may have been depleted. Changes in the concentration of electrolytes and other substances in the extracellular fluid can be readily measured by means of a sample of

plasma, whereas such changes in intracellular fluid can be discerned only by indirect research methods which are thus far too tedious to be useful in clinical therapy.

PLASMA WATER The extracellular water is further subdivided into the *interstitial water* (between the cells but outside the vascular bed) and the *plasma water* The interstitial volume is determined by subtracting the plasma volume, measured with radioiodine-tagged serum albumin (RISA) or with Evans blue dye (T-1824), from the measured extracellular fluid The *total blood volume* may be calculated using the measured plasma volume and the venous hematocrit, or, the red cell mass may also be determined directly by measuring the volume of dilution of red cells tagged with a radioisotope of phosphorus, chromium, or iron

All these technics involve the use of the dilution principle (Fig 12)

In the lean individual, *plasma volume* represents approximately 4 to 5 per cent of body weight, or approximately 6 to 7 per cent of body water Plasma volume also is more closely correlated with total body water than with body weight, and the plasma volume of the lean individual represents a higher percentage of body weight than it does in the obese individual The estimation of what the normal volumes should be is probably better arrived at by utilizing body height than body weight, and the utilization of the convention of "ideal body weight" is again helpful in this connection In the individual of average nutrition, or using the ideal weight of the lean or obese subject, the *blood volume* represents a figure ranging from 75 to 85 cc per kg of body weight Since the red cell mass represents somewhat less than one-half of the total blood volume (normal hematocrit, 46 vol. per cent), the plasma volume constitutes slightly more than half the total blood volume

The plasma volume and the interstitial volume are perhaps even more closely related functionally than are the intracellular and the extracellular volumes, and deficits in interstitial volume promptly affect the plasma volume A rapid loss in plasma volume due to hemorrhage is compensated for by the movement of water from the interstitial space into the vascular bed

Finally, it should be pointed out that the body fluid compartments are listed as such only for the sake of conceptual convenience, for there is a constant and extremely rapid exchange of water molecules throughout all areas of the body For this reason, we like to refer to the circulation of water throughout the body as the *greatest circulation*, the circulation of blood systemically as the *greater circulation*, and the circulation of blood through the pulmonary circuit as the *lesser circulation* Water comprises the major transportation system of the body, and most of the body chemical reactions go forward within this medium

The Maintenance of the Volumes of the Individual Water Compartments

In health the several water compartments are maintained at stable relative volumes, and it is of interest to consider how this is achieved In brief, the water is held by the osmotic potentialities of the various substances contained within the intracellular fluid, the interstitial fluid, or the plasma For example, the volume of the extracellular fluid depends largely upon its content of sodium chloride, especially sodium The chemicophysical structure of the extracellular fluid is built around its sodium content, an important concept which is valuable in the treatment of patients For, not only is the absolute salt content (and osmolarity) of the extracellular fluid dependent upon sodium, but sodium constitutes the principal ion responsible for the regulation of the pH of the extracellular fluid It is clear that *sodium emerges as the dominant ion of the extracellular fluid*

The normal concentration of sodium in the extracellular fluid is approximately 145 mEq/L of water (as measured in plasma water) The normal level of chloride is approximately 103 mEq/L, that of bicar-

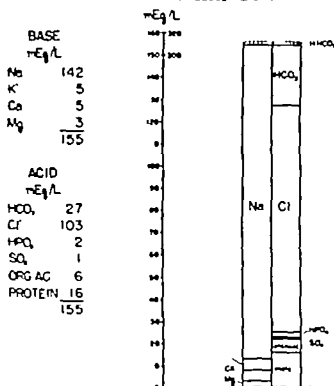


Fig 15 The milliequivalents of anion equal the milliequivalents of cations under all circumstances (From GAMBLE, J L *Chemical Anatomy Physiology and Pathology of Extracellular Fluid* Cambridge Mass., Harvard University Press 1947)

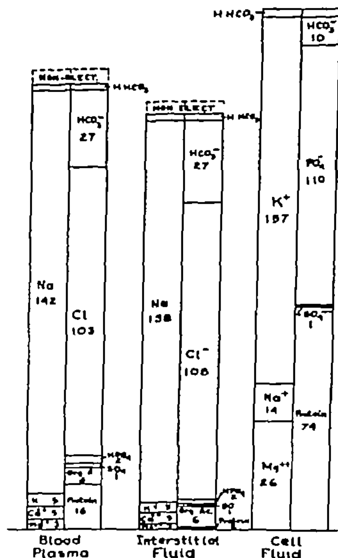


Fig 16 The relative ionic compositions of plasma interstitial fluid and intracellular fluid Sodium is the major cation of the extracellular fluid (plasma plus interstitial fluid) and potassium is the major cation of intracellular fluid Similarly chloride and bicarbonate are the principal extracellular anions whereas phosphate and protein are the principal intracellular anions. (Modified from BLAND J H *The Clinical Use of Fluid and Electrolyte* Philadelphia W B Saunders Company 1952)

bonate approximately 27 mEq/L and that of potassium approximately 3 5 to 5 mEq/L. (Fig. 15) As will be seen later when the content of salt in the extracellular fluid decreases the extracellular volume usually decreases and when the amount of salt in the extracellular fluid increases, it holds water and tends to increase the extra cellular volume

THE DARROW YANNET CONCEPT It may be seen in Figure 16 that the various body fluid compartments are essentially isotonic or iso-osmotic with plasma and with each other This is true even though the relative proportions of the different ions vary considerably from one body fluid to another Similar osmotic pressures are found in gastric juice, pancreatic juice and plasma for example, and these relationships suggest the existence of a delicate mechanism for adjustment. This mechanism by which osmolar balance is preserved between extracellular and intracellular fluid was studied by Darrow and Yannet[17] who demonstrated that water introduced by mouth or intravenously was rapidly distributed between the extracellular and intracellular fluid compartments Similarly, the introduction of sodium chloride into the extracellular compartment resulted in the movement of water from the cells into the extracellular space to preserve relative osmotic equilibrium between the extracellular and the intracellular compartments This relationship has been used in the treatment of water intoxication (due to cellular overhydration) and in neurosurgery

to reduce cerebrospinal fluid pressure by the introduction of sodium chloride into the extracellular compartment the sodium and chloride ions are not readily carried into the cells and thus they exert an osmotic force in the extracellular space to draw water from the cells

The *plasma volume* is a component, with the interstitial water, of the extracellular water compartment How, then, is the plasma volume maintained, particularly when there may be derangements in the extracellular volume?

The plasma volume is of course influenced by changes in interstitial fluid volume, but there is a strong tendency for normal plasma volume to be maintained even in the face of a body water deficit This is because of the relatively small but very important *colloid osmotic pressure* exerted by the plasma proteins, especially by albumin Therefore, while the relatively high hydrostatic pressure (32 mm Hg) at the arterial end of the capillary forces water out of the blood stream, the relatively high colloid osmotic pressure (25 mm Hg) at the venous end of the capillary tends to draw water back into the capillary (Fig 17) Again, the plasma volume is actually a portion of the extracellular fluid, and the major distinguishing feature between plasma and interstitial fluid is provided by the higher concentration of proteins found within the blood stream

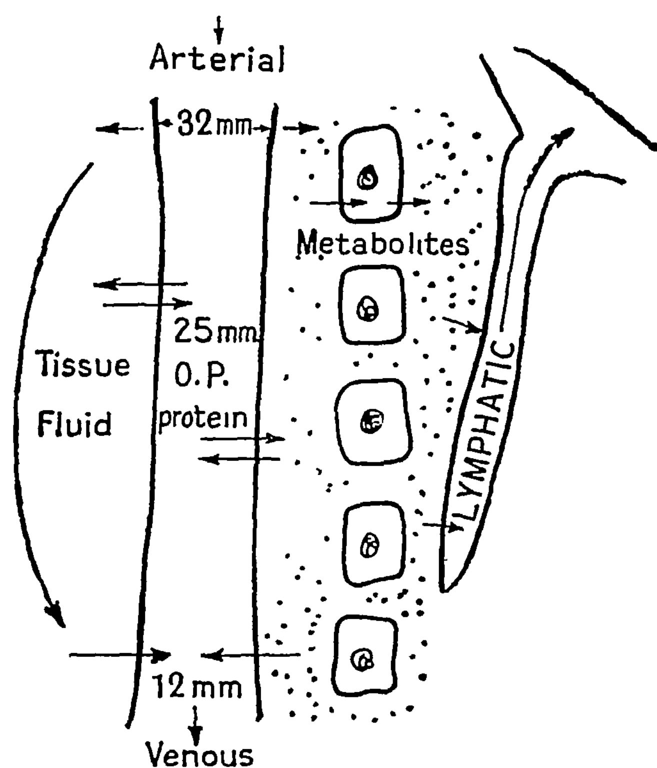


Fig 17 In essence, hydrostatic pressure forces fluid into the extravascular space at the arterial end of the capillary, and the colloid osmotic pressure of the plasma proteins (chiefly of albumin) pulls the fluid back as the hydrostatic pressure declines toward the venous end of the capillary Yet, transcapillary transfer of the constituents of plasma is a highly complex process, and it is by no means all a matter of simple diffusion (From WRIGHT, S Physiologic aspects of rheumatism Proc Roy Soc Med, **32**. 651, 1939)

INTRACELLULAR IONS (FIG 16) The major intracellular ions are potassium, magnesium, protein, and phosphates, and the osmotic force provided by these substances maintains the intracellular fluid volume relative to the extracellular volume The concentration of potassium within the cell is relatively enormous and represents a level which would be quickly fatal if in the extracellular fluid That such a release of intracellular potassium rarely occurs, except in the presence of extensive cellular destruction, attests the remarkable orderliness of the factors which regulate body fluid composition

It is unlikely that more than a small amount of the potassium contained within the cell is in ionized form Moreover, there is now much evidence that the movement of water across the cell membrane in response to osmolar effects is closely related to the metabolism of the cell In other words, the substances within the cell may exert greater osmotic pull or force at one time than at another, depending upon the metabolic circumstances existing within the cell at the time The volumes of the fluid compartments are commonly altered in disease, and in normal subjects they can be made to change by the injection of salts, water, or hormones

Body Solids

Up to this point we have dealt principally with body water and body fat In the individual of average obesity, the body water represents approximately 60 per cent of body weight and the body fat represents approximately 18 to 20 per cent of body

weight (Fig. 14) Obviously there is an additional percentage, approximately 20 per cent which is unaccounted for by fat and water This portion is referred to as the *fat free solids*, and is composed of the minerals of the body and of solids other than minerals For instance these other solids would represent the portions of the cells which were not mineral and which were not water —that is, the organic solids It should be noted here that even the very lean individual in health has about 10 per cent of body fat

The *electrolyte pools* or stores of the body, particularly those of sodium and potassium can be measured with the radioisotopes of these elements utilizing the dilution principle One injects a known amount of radioactivity or a known volume of counts and then allows this radioactivity say in the form of radiosodium, to be distributed through or equilibrated with the readily exchangeable sodium of the body A plasma sample is then drawn and the concentration of sodium in 1 ml of the sample determined By measuring the number of counts in 1 ml of plasma—and by knowing the milliequivalents *of sodium in the milliliter of plasma* and the total number of counts injected—one can solve for the total milliequivalents of sodium in which the total counts injected must have been distributed Precisely the same type of procedure may be performed utilizing radiopotassium, and the exchangeable potassium pool measured Therefore it is possible to measure or to calculate in the living subject the plasma and the blood volumes the extracellular fluid, the total body water the intracellular fluid, and the total exchangeable potassium and sodium, body fat, and fat free solids McCance and Widdowson[34] found that the minerals of the body may vary from 6 6 per cent of the body weight of the thinnest normal subject to 2 9 per cent of that of the most obese subject Moore and his associates[10] listed eight basic types of change in body composition as follows (1) *Whole tissue loss* or 'balanced starvation ' as in short periods of fasting without thirsting or such as might be observed in the presence of carcinoma of the esophagus (2) *Fat loss*, such as might occur in the presence of an inadequate caloric intake due to cancer or from dieting in obesity (3) *Water loss*, a clinical example of which might be acute gastric or intestinal obstruction, untreated (4) *Lean tissue loss with or without fat gain*, such as the muscular wasting which occurs following immobilization for the treatment of a fracture or in the final stages of starvation after the available fat has been burned This also would occur in the presence of Cushing's syndrome where lean tissue is lost but fat is gained (5) *Whole tissue gain* as seen in normal growth, and also during convalescence from a prolonged illness or severe operation (6) *Pure fat gain* (7) *Water gain*, as in heart failure, liver failure or nephrosis (8) *Lean tissue gain*, such as in athletic training or in certain stages of convalescence

Such measurements enable the clinician to appreciate better the changes in body composition which are constantly occurring in many of his patients, and will inevitably *lead to more appropriate nutritional therapy*

Acid Base Regulation

At this point it is convenient to examine the mechanisms by which the acid base balance of the body fluids is maintained

Certain Definitions

MOL AND MILLIMOL A mol of a substance comprises a gram weight of the substance equal to its molecular weight. For example, a mol of sodium chloride weighed out on the chemical balance represents, for practical purposes 58 gm of the salt (representing 23 gm of sodium and 35 gm of chloride) Since it is frequently desirable to deal with sub-units of the mol the term millimol is employed to represent 1/1000 of the mol. The amount of sodium chloride contained in a liter of extracellular water is approximately 8 5 gm , and one might estimate that

TABLE 1 RELATIONSHIPS BETWEEN MILLIOSMOLS AND MILLIEQUIVALENTS

1 mol → 1000 millimols 1 mol in solution provides 1 osmol, or 1000 milliosmols, of osmotic pressure	1 equivalent weight of a substance provides 1000 mEq The equivalent weight of a substance is determined by dividing the atomic weight by the valence For example, sodium is a monovalent ion and its equivalent weight is 23 gm divided by 1, or 23 gm In contrast, calcium is a divalent ion, and its equivalent weight is obtained by dividing the anatomic weight of 40 gm by 2, giving 20 gm

Thus, the term milliosmol is used to describe the osmotic pressure provided by ions or nonionized particles in solution In contrast, the term milliequivalent is used to denote the acid or base neutralizing potential of particles in solution However, since most of the ions in the body are monovalent ions and represent highly dissociated (ionized) salts, the total milliequivalents of acid and basic ions in a liter of plasma reflects with considerable accuracy the molar concentration (tonicity) of the extracellular fluid

the individual who has 15 L of extracellular fluid would contain in this fluid approximately 8 5 × 15 or 127 gm of sodium chloride Of course, the absolute amount of salt will vary from one person to another, though the plasma concentration is remarkably constant in health A part of the sodium in the extracellular fluid is combined with bicarbonate, and so there is always more sodium than chloride in the extracellular fluid

The term millimol is used to denote the concentration of particles in a solution, in contradistinction to the term milliequivalent which connotes the acid-base or neutralizing potential of the particles in solution (Table 1)

OSMOL AND MILLIOSMOL The mol represents the actual weight of the salt or other substance in the solution, and the *osmol* represents the osmotic pressure or force exerted in the solution by the mol of the substance Similarly, the millimol corresponds to the milliosmol

However, mols of two different substances do not necessarily provide equal osmotic pressures, since one substance may be more completely *ionized* than the other and thus may provide a greater number of particles to exert osmotic force Such would be true of sodium chloride as compared with glucose A molecule of glucose, relatively unionized, would exert approximately the osmotic force of 1 mol (1 osmol) In contrast, 1 mol of sodium chloride, a largely ionized salt, would represent almost 2 osmols, 1 from the sodium ion and 1 from the chloride ion

EQUIVALENT AND MILLIEQUIVALENT Another definition which must be understood to achieve effective practical fluid therapy is that of the *equivalent weight* of a compound and its sub-unit, the *milliequivalent* Whereas the mol and the osmol have to do with the *number* of particles in solution and with the osmotic force which they exert, the *equivalent* and the *milliequivalent* have to do with the acid base *neutralizing potential* of the element To refer to basic chemistry, an equivalent weight (1000 mEq) of a salt is that weight in grams which in a liter of water produces a *normal solution* In the case of monovalent ions, such as sodium and chloride, an *equivalent weight* of the salt (NaCl) corresponds to the *molecular weight* of the salt (58 gm) One mol of sodium chloride provides 1 equivalent weight of both sodium and chloride or 1000 mEq of each However, when the *valence* of the ion is greater than 1, such as that of calcium which is 2 (*e g* , $CaCl_2$), the equivalent weight no longer corresponds to the molecular weight of the salt Here 1 molecular weight of calcium chloride provides 2 equivalent weights of calcium and 2 equivalent weights of chloride That is, calcium, a divalent ion, can neutralize 2 monovalent ions of chloride Therefore, the ionic diagram of milliequivalents shown in Figure 15 does not precisely reflect the milliosmols

of osmotic pressure exerted by the substances represented in the diagram Nevertheless, since over 90 per cent of the ions in the extracellular fluid (chiefly sodium and chloride) are univalent, for practical purposes the sum of the milliequivalents of electrolytes reflects with considerable accuracy the millimols (and the milliosmols of osmotic pressure) of these ions This fact is useful in clinical fluid therapy When normal osmolar or osmotic pressure relationships exist in the extracellular fluid the sum of the milliequivalents of plasma chloride plus the carbon dioxide combining power in milliequivalents represents a figure of approximately 130 mEq /L If this sum is significantly less than 130 hypo-osmolarity or hypotonicity of the extracellular fluid exists, and relatively more salt or relatively less water is needed depending upon the circumstances If the sum of the milliequivalents of chloride and of bicarbonate is significantly greater than 130, relatively more water or relatively less salt is required to restore normal osmolarity Again a lowered plasma concentration of an electrolyte may reflect either a deficit of the electrolyte or an excess of water, and both situations are encountered in clinical practice

THE USE OF MILLIEQUIVALENTS INSTEAD OF MILLIGRAMS OR VOLUMES PER CENT The normal plasma electrolyte values are given in Figure 15, and no mention is made of milligrams or of volumes per cent This is because it is impossible to conduct orderly fluid therapy in the absence of a knowledge and use of milliequivalents In no other way can the relative relationships between acid and basic radicals be visualized promptly and appropriate corrections made for disorders in acid base balance and osmolar concentration

As noted above milliosmols have to do with maintaining the volume of a body fluid compartment (representing a physical process) and milliequivalents have to do with the acid base relationships of these volumes (representing a chemical process) Actually, however for the most part the same ions perform both functions The tonicity or osmolarity of the extracellular fluid is regulated by the number of particles in this solution, the acid base balance (or the hydrogen ion concentration, or pH) is regulated by the electrical charge on these various ions There must exist proper proportions between negatively charged ions (*e g*, Cl^-) and positively charged ions (*e g*, Na^+) When the proper proportion between the acid radicals (negatively charged ions or anions) is not maintained relative to the proportion of basic radicals (positively charged particles or cations), acid base imbalance results an excess of strong cations would produce alkalosis and an excess of strong anions would produce acidosis However utilizing the weak anion bicarbonate, *the total anions equal the total cations at all times* A mildly alkaline pH (7 4) results

Regulation of Blood pH

Let us now focus the discussion upon a single function that of the regulation of the blood pH or hydrogen ion concentration, since this permits a review of the factors which assist in maintaining the normal pH of approximately 7 4 Though unfolding evidence increasingly documents the complexity of this process certain principles have long been established and have proved valid The restriction of the hydrogen ion concentration to within rather sharply circumscribed limits is essential to life

What is pH?[22] Distilled water at 22 C is dissociated or split very slightly into hydrogen and hydroxyl ions This dissociation is of such a magnitude that in 10,000 000 L of water there occurs 1 gm of hydrogen (H^+) ion and 1 gm of hydroxyl (^-OH) ion. This may be expressed as an hydrogen ion concentration of 10^{-7} and an hydroxyl ion concentration of 10^{-7}, the product of these being 10^{-14} In any water solution, whether acid or alkaline, the product of the hydrogen ion and the hydroxyl ion is always 10^{-14} A completely dissociated full strength alkali would have an hydrogen ion concen

tration of 0 00000000000001 (which is more conveniently expressed as 10^{-14}, since the product of the hydrogen ion and the hydroxyl ion is always 10^{-14}), similarly, the completely dissociated strong acid could be expressed as an hydroxyl ion concentration of 10^{-14} Thus, it is clear that an expression which denotes the concentration of either hydrogen or hydroxyl ions in a solution automatically describes that of the other, since the product of the concentrations must be 10^{-14} By convention, the concentration of the hydrogen ion has been chosen to indicate the reaction (acidity or alkalinity) of a solution, and the term "hydrogen ion concentration" is abbreviated to the simple *pH* (the exponent with the minus sign dropped)

In point of fact, strengths such as those given for the completely dissociated (ionized) acid or alkali are never reached, and the acidity or alkalinity of a solution may be expressed as a pH which will generally lie somewhere between 1 and 14—the lower the pH, the higher being the hydrogen ion concentration For example, an 0 1 normal solution of hydrochloric acid could be expressed as having an hydrogen ion concentration of 10^{-1} or a pH of 1, each 10 L of solution would contain 1 gm of hydrogen ions In a 0 1 normal solution of sodium hydroxide there would occur 1 gm of hydrogen ion in each 10,000,000,000,000 L of solution, the hydrogen ion concentration being 10^{-13} or a pH of 13 An absolutely equal concentration of hydrogen and hydroxyl ions would represent a pH of 7, or absolute neutrality Actually, the pH of the body fluids is normally slightly alkaline, and the normal pH of blood is 7 4

THE MAINTENANCE OF A NORMAL BLOOD PH

In this section will be considered the blood buffers, the excretion of carbon dioxide by the lungs, and the excretion of fixed acids by the kidneys

The blood buffers Living organisms are quite sensitive to alterations in the pH of the surrounding medium and, as mentioned, they can often tolerate only slight variations from the normal hydrogen ion concentration Therefore, the regulatory mechanisms which protect the body fluids from rapid or marked changes in pH upon the introduction of acid or alkali must be sensitive indeed The basic protective mechanism is represented by renal function, since only the kidneys can eventually excrete fixed acid or basic radicals such as an excess of sodium, on the one hand, or an excess of chloride, on the other However, this represents a relatively slow process and there is a much more rapid, though less sturdy, system of buffers which is able to absorb the immediate shock when fixed acid or alkali is infused This system consists of the blood buffers, which are promptly assisted by the lungs through the retention or excretion of carbon dioxide The most sensitive and important of these blood buffers is, therefore, the *bicarbonate-carbonic acid system*

The manner in which the bicarbonate-carbonic acid buffer system functions may be better visualized by reference to Figure 15 The total sum of the plasma cations is equal to the sum of the plasma anions (acid radicals) per liter Note that if the bicarbonate ion ($^-HCO_3$) be disregarded, then the milliequivalents of cations or basic radicals are in excess of the milliequivalents of anions Note further that the number of milliequivalents of bicarbonate (largely in the form of sodium bicarbonate) is normally 27 per L of extracellular fluid, that is, there are 27 mEq of cations or basic radicals in excess of the anions or acid radicals other than the bicarbonate ion ($^-HCO_3$) *These 27 mEq of excess cations over and above the anions other than bicarbonate represent the foundation of acid-base regulation and are referred to variously as the alkali reserve, the alkaline reserve, or the available base* It is upon the alkali reserve that the normal maintenance of a slightly alkaline pH of the extracellular fluid depends The available base is measured clinically as the "carbon dioxide combining power" or the "CO_2," or the "CO_2 combining power" of the plasma (and the extracellular fluid) As an example, if one were to infuse hydro-

chloric acid into a vein, the sodium bicarbonate of the alkali reserve would combine with the hydrochloric acid to form sodium chloride and carbonic acid, with excess carbonic acid being readily excreted by the lungs (Fig. 18) In this way the dangerous strong acid (hydrochloric) is converted to a neutral salt and a weak acid Carbonic acid a mildly dissociated substance has effectively reduced the acid potential of the hydrogen ion derived from the hydrochloric acid Thus capacity to excrete or retain carbonic acid as necessary to maintain a normal blood pH, is referred to as *respiratory* or *pulmonary compensation* Actually one can infuse considerable amounts of hydrochloric acid in human beings before any measurable change is produced in the blood pH in many instances although eventually the blood pH must change if this is continued Or the opposite experiment may be done, namely the infusion of sodium hydroxide solution slowly into a vein The infused sodium combines with carbon dioxide derived from metabolic sources and here a strong basic radical is incorporated into a relatively weak or poorly dissociated alkali The sodium ion of the sodium bicarbonate thus increases the alkali reserve without significantly altering the blood pH The additional carbonic acid would be made available by a diminished minute volume of respiration with a consequent retention of carbon dioxide (Fig. 18)

Other buffers of blood While the bicarbonate-carbonic acid buffer system is the most prominent of the blood buffers the phosphate buffer system, the plasma proteins, and the buffers of the red blood cells are also of importance Furthermore it has been found that the buffering capacity exhibited by the extracellular fluid when much acid is infused is greater than would be expected were only the ions contained within this fluid compartment to be active in neutralizing the infused acid This and other types of evidence have prompted an increasing awareness that the pH of the extracellular fluid is as might be expected closely

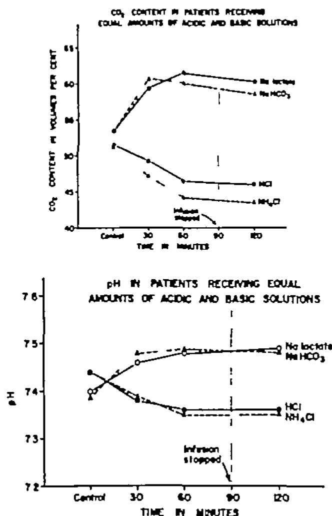


Fig 18 The relative efficacy in man of sodium bicarbonate and sodium lactate as alkalizing compounds, and of ammonium chloride and hydrochloric acid as acidifying compounds In each instance 167 mEq of the substance under study were infused in a volume of 1 L at a constant rate Each group consisted of 4 patients Sodium lactate and sodium bicarbonate were both effective alkalizing compounds, and HCl and NH_4Cl were both effective acidifying compounds (Modified from HARDY J D DAVIDSON J O JR., AND TURNER M D Further studies in body fluid metabolism II The relative efficacy in man of sodium bicarbonate and sodium lactate as alkalizing compounds and of ammonium chloride and hydrochloric acid as acidifying compounds Surgical Forum 7: 56 1957)

related to the pH of the intracellular fluid—and that the ions within the cell are apparently available for assistance in the neutralization of infused acid or alkali

In the case of the phosphate buffers the intravenous infusion of hydrochloric acid results in a combination of hydrochloric acid with disodium phosphate (Na_2HPO_4) to *form sodium chloride and monosodium phos-*

concerning the influence of various hormones upon body water metabolism, but it is only in relatively recent years that the tremendous surge of research in this field has resulted in a far better understanding of what the ultimate precise relationships are likely to be Even so, many accepted boundaries of hormonal influence in fluid metabolism are still dimly perceived, not to mention the possible vast expanse of the unknown While arbitrarily selected, the elements of the following discussion were chosen to occupy an intermediate position between material that is so new as to require further confirmation, on the one hand, and that which now is of largely historic interest, on the other

General Survey of Hormonal Influences

So far it has been indicated that the relative volumes of the body fluid compartments are regulated in large part by the electrolyte content of these volumes, and that the pH of the fluids is regulated by the relative proportions of these ions Were one to add to these considerations only the hydrostatic pressure exerted upon capillary water by the pumping action of the heart and the counter-effect of the colloid osmotic pressure of plasma, the reader might conclude that body fluid metabolism is a relatively simple physicochemical process However, there are yet to be considered the somewhat more subtle influences which regulate the body content of the electrolytes which, in turn, regulate the relative volumes of the body fluid compartments These subtle influences are often hormonal in nature and were mentioned briefly in Chapter 1 Basically, it is the kidney and, in particular, the function of the renal tubule (Fig 21) which maintains the proper amounts of salts and water in the body, the normal function of the tubule is maintained largely through hormonal influences Thus, we now move further into the exceedingly complex mechanisms which in the aggregate preserve body salt and water concentrations, in the proper volumes and at the proper pH

Virtually all endocrine substances influence water and salt metabolism either directly or indirectly (Fig 3) To begin with the pituitary, the anterior lobe of this organ secretes thyroid stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH) which influence the thyroid and the adrenal cortex, respectively *Thyroxine* is released and acts as a diuretic agent, and this effect is readily noted in the myxedematous individual given this hormone Moreover, thyroxine alters general metabolism, and this in turn also affects body composition The ACTH from the pituitary results in the liberation of a complex of active *steroids from the adrenal cortex* and these will be discussed in somewhat greater detail below The posterior lobe of the pituitary (or perhaps the adjacent hypothalamus) secretes the *antidiuretic hormone* (ADH) There is a growing body of evidence to indicate that this hormone is even more important than previously realized in the normal regulation of fluid metabolism When inadequate amounts of this hormone are secreted, the well known syndrome of diabetes insipidus results Functioning tumors of the posterior pituitary secreting large amounts of ADH have not yet been demonstrated, but an increased antidiuretic effect is often observed following operation Experimentally, one can inject a patient or an animal with large amounts of pitressin (ADH) and produce, upon the infusion of enough water, symptoms and signs of water intoxication due to the fact that the water load is not excreted, water intoxication is also encountered clinically The action of the antidiuretic hormone is, then, to increase the tubular reabsorption of water, though there is also an effect which decreases slightly the excretion of sodium and chloride The relationships of the neurohypophysis are shown in Figure 20

Epinephrine and norepinephrine also have an effect upon renal tubular function In a recent study of these effects in man Smythe, Nickel and Bradley[50] found that both depressed the urinary excretion of sodium and potassium in normal subjects Since the

glomerular filtration rate remained relatively constant despite variations in arterial pressure intrarenal vasoconstriction, and renal ischemia the change in electrolyte output was considered to be due to augmented tubular reabsorption Urine flow usually increased somewhat during the action of the two hormones and fell off sharply on withdrawal

While the chief function of *insulin* is to promote the utilization of glucose the absence of adequate amounts of insulin has a dramatic effect upon water and salt metabolism as observed in diabetic acidosis Here the utilization of fixed base to excrete the acid ketone bodies derived from incomplete fatty acid oxidation results in a loss of salt from the body with consequent dehydration despite excessive thirst and polydipsia The administration of insulin in this condition results in a rapid deposition of glycogen and with it potassium A serious hypokalemia may result during this early phase of treatment and must be guarded against provided that the low plasma potassium level is not the result of alkalosis produced in treating the previously existing acidosis It was shown by Burnell and Scribner[8] that the plasma potassium level can be made to rise by the infusion of acid and to decline by the infusion of alkali

The *gonadal hormones* have varying effects, but it is readily demonstrated that the administration of estrogens can result in the retention of sodium and water Physiologically this is commonly observed in the premenstrual tension syndrome and in clinical medicine it is seen in the treatment of patients with carcinoma of the breast with estrogenic substances The administration of androgens in treatment of this disease may also result in the retention of salt and water in addition to derangements in calcium metabolism. The hormonal alterations which result during pregnancy eventuate in a wide variety of physiologic changes and these influence water and salt metabolism as well as other functions The *toxemia of pregnancy* is surely due to hormonal effects

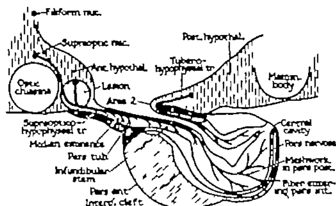


Fig 30 The anatomy of the hypothalamus and the neurohypophysis Lesions of the hypothalamic region may produce diabetes insipidus due to inadequate secretion of pitressin (ADH antidiuretic hormone) (From Fisher C Ingram W R, and Ranson S W *Diabetes Insipidus and the Neuro-Hormonal Control of Water Balance A Contribution to the Structure and Function of the Hypothalamico-Hypophyseal System* Ann Arbor Edwards Brothers Inc., 1938)

though this complex pathologic state has never been satisfactorily explained

Parathormone has to do with the regulation of calcium and phosphorus metabolism (Fig 229)

The Adrenal Cortex: Principal Hormonal Organ in Water and Salt Metabolism (Figs 234 and 235)

Since the rôle of the adrenal cortex in fluid metabolism was mentioned in some detail in Chapter 1, the present discussion will include only the more general features of the adrenocortical influence

More than 30 different steroids have been isolated from the adrenocortical secretion, but the major portion of the corticosteroid output appears to be in the form of hydrocortisone (F) This and most of the other corticosteroids have particularly to do with the metabolism of glucose and of nitrogen but they nevertheless have an influence upon water and salt metabolism. This is shown by the fact that following total adrenalectomy the administration of cortisone or hydrocortisone results in adequate stabilization of fluid metabolism in most patients In the occasional patient however, it is necessary to administer desoxycorticosterone also This brings us to consideration of the

recently isolated hormone *aldosterone*, which has a profound effect upon water and salt regulation but virtually no rôle in nitrogen and glucose metabolism This remarkable adrenal steroid, only recently isolated, is now considered to have normally a major rôle and possibly the major rôle in water and salt metabolism The secretion of this substance is increased following operation, and it may be chiefly responsible for the excretion of potassium and the retention of sodium and perhaps chloride

The effects of cortical hormones on fluid metabolism may be generally summarized as follows first, there is an effect on renal tubular function which influences the rate and extent of water excretion Second, as a rule, the adrenocortical hormones result in an increased tubular reabsorption of sodium, with the consequence that there is a retention of water due to the osmotic effect of the retained cation Nevertheless, it has been shown that a particular hormone may cause a different effect in the same individual under a different set of physiologic circumstances Third, the administration of adrenocortical hormones or their secretion in the body almost invariably results in an increased excretion of potassium, due both to a cellular depletion (increased mobilization) of this ion and, probably, to an influence on the tubular reabsorption of potassium Finally, the adrenocortical hormones have a marked effect upon the transfer of potassium across the cell membrane, probably by altering cellular metabolism

In the presence of adrenocortical insufficiency the cells tend to become overhydrated and water intoxication may ensue, in contrast, the administration of adrenocortical hormones greatly reduces the susceptibility to water intoxication Again, although the administration of adrenocortical hormones may in the same individual induce at one time sodium retention and at another time sodium excretion, the usual effect of these hormones on potassium is to increase the excretion of this ion It is difficult to produce a potassium deficiency in dogs by dietary means, but this objective is fairly readily achieved by the administration of desoxycorticosterone or other adrenocortical hormones

TYPES OF ADRENOCORTICAL INSUFFICIENCY

It is important to make the distinction between acute adrenocortical insufficiency and chronic adrenocortical insufficiency (p 578) In acute adrenocortical insufficiency, such as might follow the resection of a large functioning tumor or bilateral adrenalectomy, the signs of adrenocortical insufficiency are notably different from those in the chronic form and they come on much more rapidly, before marked changes in body water and electrolyte concentrations have occurred The patient who goes into *adrenocortical crisis* within 48 hours following resection of adrenal tissue manifests hyperthermia, hypotension with a rapid heart rate, apprehension, anorexia, and often nausea and vomiting However, if the individual slips into failure more slowly or subacutely, as might result from the too rapid withdrawal of replacement therapy following subtotal adrenocortical resection, there is more time for the plasma sodium level to decline and for the nonprotein nitrogen (NPN) level of the blood to rise, with associated mental confusion There may be no rapid change in blood pressure at this stage

Finally, in the patient who has had chronically inadequate but life-maintaining adrenocortical function there will have occurred large losses of sodium, chloride, and water, with resulting weight loss and general debility The plasma sodium and chloride levels will be low There will be a diminished blood pressure level, an elevated plasma NPN level, a low blood sugar level due to defective carbohydrate metabolism, and an elevated potassium level Instead of hyperthermia, as seen in acute insufficiency, hypothermia is usually present in chronic adrenocortical insufficiency As sodium is lost, water moves into the cells with a resulting relative increase in the state of cellular hydration This cellular overhydration increases the susceptibility to water intoxi-

cation, and the administration of cortical hormones reduces this susceptibility, as noted previously. The administration of desoxycorticosterone in adrenocortical insufficiency restores the extracellular fluid volume, partially at the expense of the intracellular fluid volume.

FACTORS WHICH MODIFY THE EFFECTS OF ADRENOCORTICAL HORMONES. The administration of desoxycorticosterone in patients with Addison's disease may result in the development of edema which this hormone is much less likely to produce in normal subjects. This would appear to imply an antagonism between the different cortical steroids in their effect on water and salt metabolism. Moreover, it has been demonstrated that in adrenal insufficiency there is an increased tubular reabsorption of water and, in the opinion of Gaunt and Birnie,[71] this accelerated reabsorption of water by the renal tubules is probably due to an increased sensitivity to, and/or an increased blood level of the posterior pituitary antidiuretic hormone (ADH). These workers believe that there is probably not necessarily an increased rate of production of ADH in adrenal insufficiency but that there may be a decreased rate of inactivation of the substance, since in adrenal insufficiency the liver may not be able to inactivate this hormone in a normal fashion.

As regards the effect of adrenocortical insufficiency upon acid base balance (in addition to the acidosis which results from the over all loss of sodium) there is evidence that following adrenalectomy the ability of the kidney to conserve base by the exchange of hydrogen and ammonium ions may be impaired.

Renal Function

Rôle in Maintenance of Volume and Composition of the Body Fluid Compartments

The kidney is the primary organ in the maintenance of the normal volume and composition of the extracellular fluid and, through this volume the intracellular fluid. In addition, the kidney of course excretes waste products, and the importance of this activity is quickly appreciated when renal function is absent. However, we wish first to direct attention to the kidney's rôle in water and salt metabolism.

Let us begin by noting that the tubules of the kidney reabsorb approximately 180 liters of water (plasma filtrate) per day and selectively reabsorb those electrolytes and other materials (glucose, for example) which the body requires. Should the kidney tubules fail to reabsorb most of the water which is filtered, the individual would be dead within a very few minutes due to water loss and diminished circulating blood volume. Clinically, the importance of the reabsorption of water is apparent in patients with diabetes insipidus: because of an inadequate amount of posterior pituitary antidiuretic hormone (ADH), large amounts of water are lost through the renal tubules in the form of a dilute urine. The administration of pitressin reverses the process to increase water reabsorption in the renal tubule and, should the individual continue drinking enormous volumes of water at the previous rate, water intoxication would ensue. Again, water intoxication even in these circumstances is difficult to produce if sufficient amounts of sodium chloride are given the patient, or if an adrenocortical hormone and in particular desoxycorticosterone (or aldosterone) is administered. Therefore, while it is essential that the glomerular filtrate pass down the tubule (Fig 21) to permit the excretion of waste substances which would prove fatal if retained in sufficient concentrations it is equally essential that the kidney reabsorb most of the water. This it normally does except for the formation of from 1 to 2 L of urine on a daily fluid intake of from 2 to 3 L.

A second exceedingly important function of the kidney is to reabsorb sodium and chloride, as well as other ions. Were it not to do this, as is the case in certain forms of "salt-losing nephrosis," the body would rapidly be dehydrated due to the loss of salt

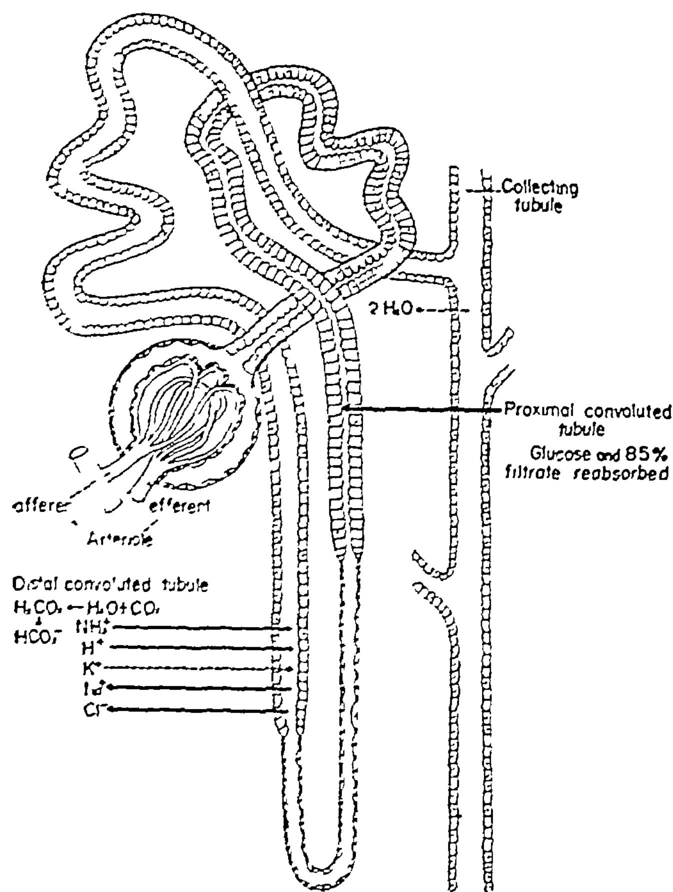
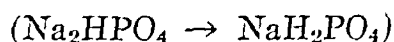


Fig 21 Glucose and 85 per cent of the filtrate are reabsorbed in the proximal convoluted tubule In the distal convoluted tubule, sodium and chloride are reabsorbed and some potassium is reabsorbed, here ammonium and hydrogen ions are produced to combine with anions, thus replacing sodium and conserving this fixed base (Modified from MERRILL, JOHN P *The Treatment of Renal Failure* New York, Grune & Stratton, Inc, 1955)

which would ordinarily "hold" water within the extracellular space An example of this is the massive diuresis and salt loss which may accompany the resumption of renal function following the oliguria observed in lower nephron nephrosis However, we agree with others that if fluid intake has been strictly limited during the oliguric period the "diuresis" is not often remarkable

In addition to the excretion of waste products and the maintenance of the body stores of water and electrolytes, the kidney has a critical rôle in the maintenance of acid-base balance This has been touched upon previously but certain points may be further emphasized here Whereas the blood buffers and the pulmonary excretion or retention of carbon dioxide could temporarily ward off threats to the normal blood pH, eventually the kidney must excrete an excess of fixed acid or alkali Accordingly, a crucial function that protects the reaction of the body fluids is the *renal conservation of base* Ordinarily the kidney stabilizes the alkali reserve (the carbon dioxide combining power) at a level of from 25 to 27 mEq/L of plasma or extracellular water Similarly, the respiratory system participates by stabilizing the plasma carbonic acid level at from 1 25 to 1 35 mEq/L And, as we have seen, the normal ratio of the bicarbonate bound base to the carbon dioxide level, being 20 1, results in the normal pH of 7 4

For the kidney to maintain the normal alkali reserve at 27 mEq/L it is necessary primarily to conserve fixed base, chiefly sodium This is done in three ways First, base is conserved by the conversion of the dibasic to the monobasic phosphate



$$(Na_2HPO_4 \rightarrow NaH_2PO_4)$$

by the substitution of an hydrogen ion for a sodium ion and the reabsorption of the latter Second, base combined with inorganic acids in blood may, in the tubules, be replaced by hydrogen ions, the acid is then excreted in the free form and the base is reabsorbed Third, the kidney forms ammonia which it substitutes for fixed base in the neutralization of acids excreted in the urine

FUNCTIONAL ANATOMY OF THE RENAL TUBULE The fluid in Bowman's space of the glomerulus has the same composition as does the extracellular fluid, but as this filtrate proceeds down the renal tubule the constituents are altered by the living cells of the tubule Performing actual work, they cause particles of both an inorganic and an organic nature to *migrate from a region of lower osmolar concentration to a region of higher concentration*, exactly the opposite to what the direction of flow would be were the process entirely passive or osmotic in nature In the proximal tubule the filtrate is

approximately the pH of plasma (slightly alkaline), but in the distal tubule the filtrate usually becomes acid in reaction because the strong basic inorganic ions (particularly sodium) are reabsorbed and hydrogen ions and the weak ammonium ions substituted When the kidneys can no longer substitute a sufficient quantity of ammonium and hydrogen ions to permit conservation of the basic cations such as sodium, fixed base must neutralize the inorganic phosphates and sulfates, in addition to organic acid radicals and this base is lost to the body, reducing the protective alkali reserve Moreover, as the extracellular sodium—the foundation of the extracellular fluid structure—is lost, so is water also lost.

Whereas the pH of the plasma is normally 7 4, the urine is usually acid and a pH as low as 5 is not uncommon, for the kidney tolerates marked shifts in reaction without injury Pitts[16] estimated that more than a pound of sodium salt is conserved by the tubules each day The proximal tubule is responsible for the reabsorption of sugar, phosphate, sodium, part of the chloride, and a portion of the water The distal tubule is likewise concerned with water reabsorption and with the conservation of base (Fig 21)

Practical Measurement of Renal Function[37]

The parts of the nephron may be tested separately and it is important to know which part is being tested since differential values may be of aid in diagnosis Furthermore it is important to realize that certain kidney functions may be normal when other functions are seriously impaired From the urea clearance and the blood NPN concentration one may gain a gross but practicable evaluation of *glomerular filtration rate* The measurement of the maximal urinary specific gravity, the ordinary "concentration test" utilizing a period of dehydration, serves as a measure of *tubular reabsorptive capacity* Finally, the fractional excretion of phenol sulfonphthalein (PSP) serves as a measure of *tubular excretory capacity*

As an illustration that one function may be normal when other components of renal function are diminished, Merrill[37] has pointed out that with glomerular disease such as occurs in glomerulonephritis the urea clearance, blood NPN, and PSP tests may be abnormal, while the concentrating ability remains relatively good (1 020 to 1 024) In contrast, in the course of pyelonephritis in which the lesions begin in the distal convoluted tubule where much water is normally reabsorbed, the concentration test is impaired early, while the blood NPN, urea clearance and even the PSP may still be relatively unaffected Therefore, to adequately judge renal function prior to operation all tests may be indicated when there is a reasonable doubt regarding the adequacy of renal function to support the patient through the contemplated surgery In conclusion, if the specific gravity measurement of a single specimen of urine is above 1 020, it usually suggests fairly adequate distal tubular function In our own experience, a low specific gravity—and above all if this remains fixed—is a finding to be viewed with the most serious concern in patients upon whom one plans to perform major surgery

Two other "function tests" which afford much useful information are the intravenous pyelogram and the indigo carmine excretion rate The visualization of the kidneys, ureters and bladder by means of intravenous pyelography depends upon the ability of the normal kidney to concentrate the various iodine compounds which may be used for this type of roentgenography Many urologists consider this one of the better indices of adequate renal function However, for maximum information from the study it is important to know which preparation was administered, since diodrast is excreted chiefly by the renal tubules and skiodan by the glomeruli Kidneys that are unable to concentrate to a specific gravity above 1 014 during a concentration test usually are un-

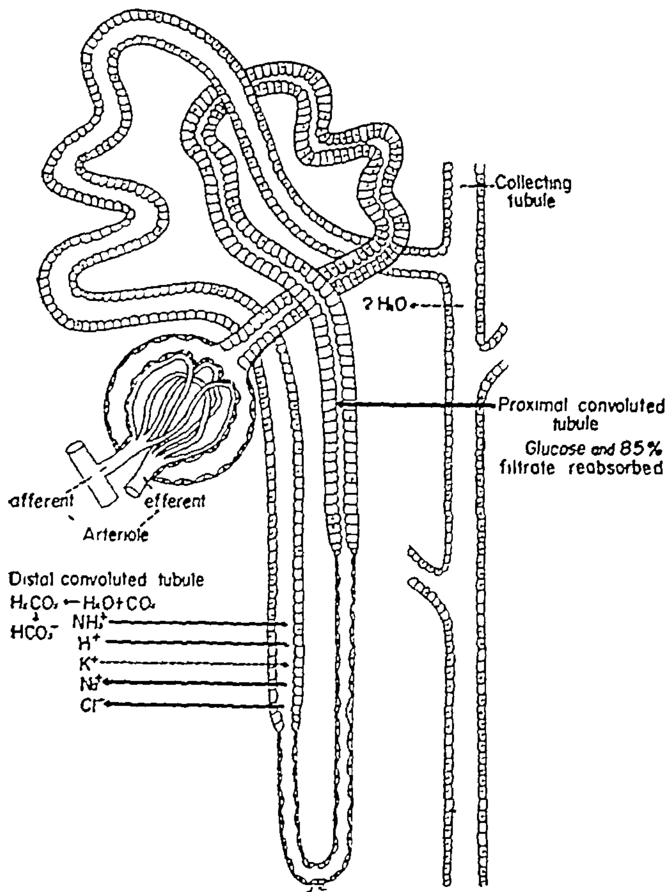


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able to concentrate iodine compounds sufficiently to afford good visualization on pyelography

The indigo carmine test measures the functional capacity of the kidneys by determining their ability to excrete the injected dye The intravenous injection of 5 cc of a 4 per cent solution of indigo carmine is accompanied by cystoscopic examination of the urine and the ureteral orifices When the kidneys are normal the dye appears as a pale blue jet from each ureteral orifice in from 3 to 8 minutes, and within 30 to 60 seconds the color changes to a deep blue Renal impairment is evidenced by a delay in the appearance of the dye in the ureters and by a less intense shade of blue

In summary, like the liver, the kidney has many subtle functions and a variety of function tests are required to measure the various facets of the activity of this remarkable organ The three major functions of the kidney are to eliminate waste, to maintain the proper state of body hydration, and to regulate acid-base balance Renal function tests may indicate the type and the extent of renal damage, but they usually do not indicate the nature of the fundamental disease process, which is more readily diagnosed by means of the clinical picture, the urinary sediment, and special examinations of the urine as well as roentgenograms of the kidneys The normal adult must secrete a minimum of from 400 to 500 ml of urine each 24 hours in order to eliminate the average of 35 gm of solids representing waste products If renal function is impaired, an even larger volume of urine formation is necessary to prevent uremia, and eventually even 2500 ml of urine per day may be inadequate to avoid uremia in far advanced renal failure

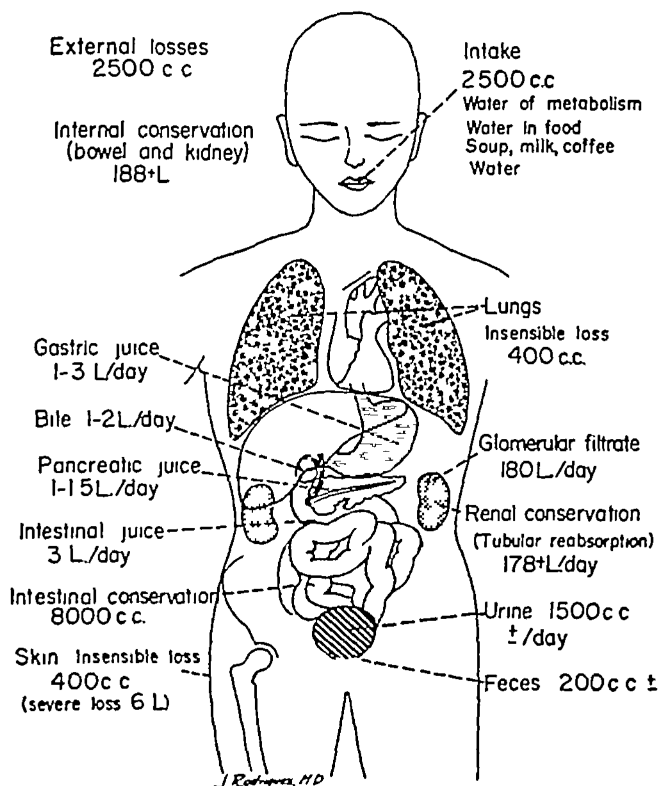


Fig 22 The gross intake-output record reveals little concerning the tremendous fluid movements which take place within the body continuously

Daily Water Balance

In practical daily fluid therapy, the physician is perhaps more concerned with the more narrow concept of daily water balance—that is, the intake-output chart—than he is with the more general problem of water and electrolyte exchanges within the areas of the body itself, such as the renal and intestinal conservation of fluid The list below gives representative and approximate values for an average person in a moderate climate at bed rest Note particularly the relatively large volume of water contained in solid foods and that derived from food oxidation

Water Intake	cc
Drinking water	700
Coffee, milk, soup	800
Water contained in solid foods	700
Water from oxidation of hydrogen in protein, fat and carbohydrate	300
Total	2500

Water Output	cc
In urine	1500
In feces	300
Insensible loss through skin and lungs	700
Total	2500

Actually, of course, the amounts given for the various sources of water intake and water output would vary from one person to

r and in the same person from day

Furthermore, the person need not ; precisely the same volume of water ay that he took in that day, but over od of a number of days the amount er taken in must equal the output, otherwise the patient must either lose n weight—and the weight of an indi- in health is remarkably constant he individual would excrete on a given nly a relatively small number of the e molecules of water ingested on that The half time of ingested water mole- is from 9 to 11 days

ROXIMATE LOSSES FROM VARIOUS ROUTES ielpful in replacing fluid losses to have idea concerning the approximate vol which may be lost from various es, and approximations for a 24 hour d are given below and in Figure 22

tric juice	1000 to 3000 cc
	1000 to 2000 cc
creatic juice	500 to 1500 cc
er small bowel fistula	Up to 8 L
iting in small bowel obstruction	Up to 8 L (not including losses into bowel lumen that are not vomited)
at	400 to 6000 cc at extremes of temperature
iva	1500 cc
estinal juice	3000 cc

iese are, again, only approximate vol s. Pyloric obstruction increases gastric etion, and one may upon occasion aspi from 5 to 6 L of fluid from the stomach 24 hour period, far beyond the range tioned in the table above The impor- e of renal reabsorption or conservation ater has been mentioned, but it is also ortant to appreciate that gastrointes- l conservation of water amounts to 8 r more each 24 hours quite enough to se serious illness and possibly death, e the entire amount to be lost from the y suddenly

Types of Fluid Imbalance

CLASSIFICATION As a working outline, most states of fluid imbalance can be defined within the following categories water and/or salt depletion (pure or mixed), water and/or salt excess (pure or mixed), acid base imbalance with acidosis (respiratory or metabolic) or alkalosis (respiratory or metabolic), and deficits of other important ions such as potassium, calcium, and magnesium

Water and/or Salt Depletion

PURE WATER DEPLETION Although severe states of pure water depletion may be encountered among shipwrecked individuals and among those lost in the desert, in clinical practice pure water depletion is rarely encountered except in patients who cannot swallow or who are too weak to do so Thus *clinical losses are almost always mixed losses* If water is available and the individual is able to swallow, simple habit or the more complicated thirst (derived from osmoreceptors of the hypothalamus?) usually results in the ingestion of an adequate amount of fluid

It will be appreciated that insensible fluid loss and obligatory urine excretion do not stop with the cessation of water intake, and hence the individual incurs a deficit of at least a liter per day Even in the individual anuric because of renal disease, the insensible loss continues at the rate of from 600 to 800 cc per day regardless of intake To put this another way, if the water intake is 1000 cc per day and the urine volume 1000 cc, there occurs a water deficit equal to the volume of the insensible fluid loss plus the loss by stool

Pure uncompensated water loss from the extracellular fluid compartment by the formation of urine by insensible vaporization and by stool will deplete the extracellular fluid space, with resulting hypertonicity of this space A shift of water from the intracellular fluid compartment to the extracellular fluid compartment will occur to maintain *relative* (but not normal) osmolar

equilibrium Simple water loss results, therefore, in a depletion of both the intracellular and the extracellular fluid compartments in approximately equal proportions Complete absence of water intake for longer than five or six days will result in a weight loss of from 5 to 7 kg and death will soon ensue, this eventuality occurring more quickly in infants than in adults because of the narrow margin of reserve and greater rate of water turnover in infants In pure water loss, the plasma sodium and chloride levels and the NPN level are elevated

In an experimental study involving human volunteers, it was found by Black, McCance and Young[7, 35] that an *intense thirst was the initial symptom in pure water depletion* There followed dryness of the mouth and difficulty in swallowing, the urine volume fell to a minimum, and the urine became as concentrated as the renal powers of the individual would allow Since the urine volume could be little less than 500 cc per 24 hours to excrete the daily load of approximately 35 gm of solids, such a water restriction imposed a severe load upon the kidneys

Black and his associates found in their experimental subjects that weakness was progressive but was not marked until three or four days had passed Thereafter, as the dehydration progressed, the patient became confused, and his mental faculties were eventually seriously impaired In these studies the plasma sodium level was increased by 30 mg per 100 cc (13 mEq per L) after from three to four days It was suggested that death in severe water depletion may be the result of an excessive rise in body fluid osmolarity

Marriott[31] has emphasized that there may be little hemoconcentration and shrinkage of the plasma volume at levels of water depletion below 6 per cent of body weight

Despite continued renal filtration at a reasonably normal level, the concentration of urea in the blood increases in simple water depletion, though the resumption of water intake promptly restores the individual t a normal state

EXPERIMENTAL WATER DEPLETION VERSU MIXED WATER AND SALT DEPLETION Elkintor Danowski and Winkler[18] produced sever water depletion in dogs by restricting th water intake and at the same time dehy drating them by giving a solution of glucos and urea intravenously It was found tha marked dehydration resulted in a dimin ished cardiac output, plasma volume, cir culation rate, and mean arterial pressure, but that peripherovascular collapse did not occur In further studies it was shown that surprisingly little peripheral circulatory failure occurred in severe chronic water depletion in the dog However, *in sharp contrast to simple water depletion, the loss of both salt and water resulted in marked impairment of circulatory efficiency* Changes in extracellular volume alone did not appear to explain these differing circulatory reactions It was concluded that extracellular volume *per se* is only one of the factors that affect plasma volume, and that it is not necessarily the most significant one It was further concluded that the amount of salt in the extracellular fluid is highly important in maintaining circulatory efficiency, regardless of what the total volume of the extracellular fluid may be

PURE SALT DEPLETION Pure salt depletion usually occurs in individuals who are placed on stringent salt restriction with unlimited water intake, such as the low-salt diet commonly used in heart failure or, in surgical patients, the replacement of body fluid losses with only salt-free solutions Clinically, however, even in "pure salt depletion" there is usually some water loss Therefore, to examine the effects in man of pure salt depletion *per se*, McCance[33] studied this problem experimentally in four human subjects who underwent prolonged periods of sweating without limitation of the ingestion of water but with the dietary sodium intake carefully restricted It was found that the

renal excretion of sodium was rapidly reduced when the sodium content of the plasma fell below normal, and that it required a week of sweating, with sodium intake restricted, before evidence of a marked salt deficit appeared. After a significant degree of sodium depletion had been produced, the studies were prolonged for several more days and lassitude, apathy, anorexia, and nausea were noted in all experimental subjects, *though none complained of thirst* This is an important clinical point of differentiation between relatively pure water depletion and relatively pure salt depletion, since the stimulus for thirst is considered to be a rise in osmolar concentration of the body fluids surrounding the osmoreceptors (cells in the hypothalamus that are sensitive to changes in osmolarity and which regulate the secretion of ADH) Where only salt is lost, the osmolarity (tonicity) of the body fluids is reduced, and there would not necessarily be a stimulation of the osmoreceptors to produce the sensation of thirst.

It has been seen from the experiments of Elkinton and his associates that salt depletion seriously affected circulatory efficiency, and it is of particular interest that in McCance's studies *the ingestion of water alone failed to produce a diuresis in the subjects who had been specifically depleted of salt*

In contrast to simple water depletion, in which there is more or less equal relative or percentage loss from the intracellular and the extracellular fluid compartments, the loss of sodium chloride from the extracellular space results in hypotonicity of this compartment and water then flows into the intracellular space, resulting in overhydration of the cells If the patient depleted of sufficient sodium chloride (extracellular) be given a large volume of water, the relatively higher osmolar concentration in the intracellular compartment may cause an excessive flow of water into the cells and produce water intoxication.

To recapitulate, the findings in pure water depletion differ considerably from those in pure salt depletion. *Thirst* may be marked in pure water depletion but slight or absent in pure salt depletion. The *urine volume* is markedly reduced in pure water depletion, but is fairly well preserved until late in the course of pure salt depletion *Sodium chloride* is usually present in the urine in pure water depletion, but is largely absent in pure salt depletion *Vomiting* and *cramps* are usually not present in pure water depletion, but are often marked in pure salt depletion. *Weakness* and *orthostatic fainting* are not prominent features of pure water depletion, but are prominent aspects of pure salt depletion The *plasma volume* is well preserved until late in pure water depletion, but is promptly reduced in pure salt depletion. Similarly, *hemoconcentration* is not an early feature of pure water depletion, but is a prominent finding in pure salt depletion The *blood pressure* is well maintained for prolonged periods of pure water depletion, but it falls rather quickly in pure salt depletion The *mode of death* in pure water depletion is obscure but may be due to a rise in the osmolar concentration of the body fluids, whereas death in pure salt depletion is usually due to peripheral circulatory failure (shock)

MIXED WATER AND SALT DEPLETION Under clinical circumstances, it is usually a combination of water and salt depletion that is encountered. This loss may take the form of the fluid and salt lost by vomiting or diarrhea, or by drainage from various types of fistulas. It may also be due to excessive sweating in the presence of febrile illnesses, or to the loss through the skin and wounds in burns Since the losses involve both salt and water, the clinical picture does not reflect either pure salt loss or pure water loss but is rather nonspecific Nevertheless, if a sufficient volume of fluid has been lost one does find anorexia, weakness, and peripherovascular collapse. Thirst may or may not be a prominent feature.

It is now generally appreciated that a common way in which a mixed water and

salt depletion is produced clinically is that of placing a Levin tube in the stomach with constant suction and then allowing the patient to drink unlimited quantities of water This results in the aspiration of the ingested water and along with it considerable amounts of sodium chloride and potassium This depletion of body salt causes a loss of additional water from the extracellular compartment, since the salt is no longer present to "hold" the water in the body

Water and Salt Excess

WATER EXCESS A relative water excess of course obtains in the presence of salt depletion without water depletion, but at this point we have in mind an *absolute water excess* which may be produced in patients who are given water but cannot excrete this fluid This can result in water intoxication due to overhydration of the cells, such as may occur in the immediate postoperative period when renal water excretion is physiologically diminished Or, it can be produced by giving a subject pitressin (ADH) and then giving a large water load Among the conditions which predispose to the development of water intoxication are the following (1) adrenocortical failure, due both to salt depletion in the extracellular space and to the absence of the adrenocortical hormones for the regulation of salt and water volumes of the extracellular compartment relative to the intracellular fluid compartment, (2) acute renal "shutdown" or diminished renal function due to the excessive loss of extracellular electrolytes, as seen in the "low sodium syndrome" of heart failure therapy and other similar circumstances, and (3) following trauma or operation, as mentioned above, where the secretion of ADH may be increased

The syndrome of *water intoxication*, due to excessive body water without proportional salt content, was first described in 1922 by Weir, Larson and Rowntree,[56] who noted convulsions in a patient with diabetes insipidus who continued his usual fluid intake after polyuria and polydipsia had been controlled with posterior pituitary extract Subsequently this phenomenon was reproduced in animals, and it was demonstrated that the seizures were related not only to the amount of water ingested but also to the concentration of extracellular ions The administration of sodium chloride was shown to reverse or prevent the syndrome, and it has since also been found that the administration of adrenocortical hormones also greatly diminishes the facility with which the convulsive seizures of water intoxication are produced Zimmermann and Wangensteen[58] reported a series of 17 surgical patients in whom water intoxication was considered to have occurred in the early postoperative period The clinical manifestations consisted of convulsive seizures following operation, associated with a dilution of extracellular electrolytes The water balance was strongly positive in most of these subjects, and in all but one instance the convulsions occurred between 12 and 48 hours following the operation The intravenous administration of hypertonic sodium chloride solution was effective in restoring normal osmolar concentration and resulted in prompt clinical improvement

Correction of water excess The most direct treatment of water excess would be to reduce the total volume of water in the body rather than merely to add salt to balance the excess water To achieve this end, Hammond and his associates[22] have infused mannitol to produce diuresis in patients with a low plasma sodium level due to excessive water retention following valvulotomy D'Angelo and his group[14] have used intravenous alcohol it appears that the alcohol suppresses the secretion of ADH Such therapy avoids the distinct hazard of giving additional salt to the cardiac patient to restore normal extracellular salt concentration and osmolarity

SALT EXCESS Aside from the relative salt excess which is present when there is a "pure water depletion," there is occasionally an absolute salt excess in patients whose ex-

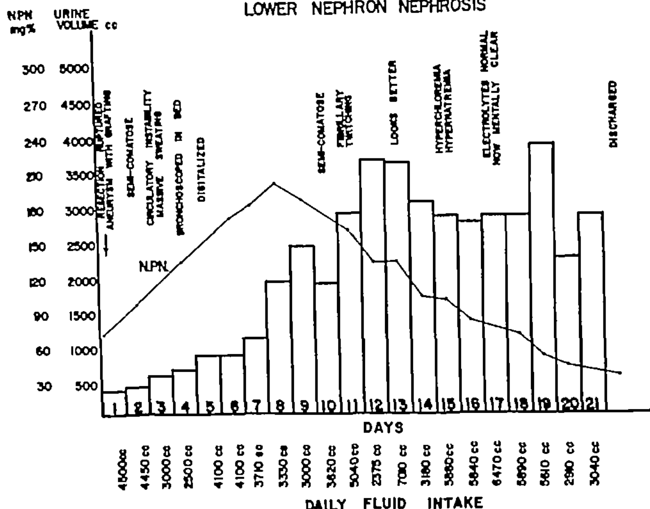


Fig 23 This patient (see also Fig 169) had a period of marked azotemia and at times he was virtually comatose He was not long hypotensive during surgery but he had had several periods of shock prior to that time A prominent feature of his case was the massive sweating, even in an air-conditioned room Daily weights were not available and fluid therapy had to be estimated on the basis of clinical evaluation and blood chemistry values. Despite intakes ranging from 2.5 to 7 L. per day he developed hyperchloremia and hypernatremia, which responded satisfactorily to further nonelectrolyte-containing fluid The nonprotein nitrogen (NPN) reached a level of 200 and then subsided Potassium intoxication was not a serious hazard after the first 96 hours He eventually returned to full employment

tracellular fluid volume (and probably the intracellular fluid volume) is actually excessive as evidenced by pitting edema. Such patients may exhibit a plasma sodium level of 160 mEq/L (normal, 145 mEq/L) and a plasma chloride level of from 120 to 130 mEq/L This represents a markedly elevated sodium and chloride concentration in the extracellular fluid, the precise genesis of which is not clearly known. We first encountered such instances in a patient with an extensive thermal burn (Fig 60) and in a patient with a pancreatic fistula, both of them had suffered prolonged hypotension and presumably had sustained some subtle qualitative alteration in renal tubular function, since both were excreting considerable volumes of urine in the presence of these high plasma levels of sodium and chloride and both were clinically edematous. More recently, however, this phenomenon was encountered in a patient whose ruptured abdominal aneurysm had been successfully grafted (Fig. 23) In this individual it appeared that simple dehydration was the cause of the markedly elevated plasma sodium and chloride levels, and prompt im

provement accompanied the infusion of additional salt-free solution

Several different types of lesions, presumably in the brain (though kidney lesions could not be excluded), were recorded by Allott[2] in 1939 He reported his cases as representing sodium and chloride retention without renal disease In four of the five patients an autopsy had been performed, and in each a brain lesion was demonstrated In 1948 Sweet and his associates[53] reported gastrointestinal hemorrhages, hyperglycemia, azotemia, hyperchloremia, and hypernatremia (increased plasma sodium level) following frontal lobe lesions in man In 1952 Cooper and Crevier[12] reported electrolyte abnormalities observed in association with brain lesions, and for this reason they described the findings as representing "neurogenic" hypernatremia and hyperchloremia It was suggested that these abnormalities were produced by damage to a cerebral osmoreceptor mechanism which resulted in defective posterior pituitary function However, in the first of our cases cited above there was no gross evidence of brain damage at autopsy, the patient whose ruptured aneurysm had been resected lived, but his hypernatremia and hyperchloremia appeared to have been due to an inadequate water intake *under the clinical circumstances* Therefore, it is always important to be certain that elevated sodium and chloride concentrations are not due to simple water deficiency, for this can be treated—and one suspects that a water deficiency, absolute or relative, may be a common cause of these elevated plasma electrolyte concentrations

General Comments on Edema

The accumulation of water and salt, in combination, in the body, whether generalized or in only one part, is referred to as representing a state of edema The presence of edema is often apparent on clinical observation, as reflected in the pitting which may be demonstrated in the [illegible] cardiac decompensation On the [illegible] d, the edema may not be readily demonstrable clinically except through weighing the patient. In fact, by utilizing daily weight measurements one employs one of the most practical methods for the management of the cardiac patient Edema not apparent on clinical examination is often referred to as subclinical or larval edema, and the individual can retain several liters of water before pitting edema becomes apparent This can also be observed in a majority of surgical patients who receive from 2 to 3 L of fluid intravenously for the first several days following surgery, *particularly if a considerable proportion of this fluid contains sodium chloride* (Fig 7). If such patients are weighed for several days preoperatively and these measurements then continued for several days postoperatively, it will be found that during the first day or so following operation there may be an increase in body weight due to fluid retention, following which most patients will lose several kilograms due to the loss of this water plus both fat and lean tissue (Chapter 1) Weight gain due to fluid retention is even more striking when a newborn is given an excess of salt solution, since the neonatal kidney is relatively inefficient in excreting sodium chloride Still another common clinical example of the retention of infused sodium chloride solution is that observed in the treatment of patients with extensive thermal burns (Figs 54, 55, and 56) Massive fluid administration is required to offset the outpouring of fluid which results in characteristic swelling of the part representing "burn edema" or "wound edema" Actually, such an outpouring of fluid occurs adjacent to almost any injury, such as traumatic contusion of the extremity or around a fracture, though blood also is e[illegible]vasated in t[illegible] [illegible]stances This [illegible] on of fl[illegible] [illegible]g injury is [illegible] [illegible]ently [illegible] hydrate the [illegible] [illegible]re, to [illegible] circulating [illegible] c, an[illegible] shock A [illegible] [illegible]atic [illegible] [illegible]bcut [illegible] [illegible]affi

chloride moves into this fluid and depletes the extracellular space, and salt-loss shock may result

MECHANISMS OF EDEMA FORMATION The few examples given above serve to indicate that the formation of edema fluid is a common circumstance in surgical practice, and they serve also to emphasize that the formation of edema has important physiologic significance. It is appropriate now to review some of the more common mechanisms of edema formation, bearing in mind the while that these mechanisms intermesh and that the formation of edema under any particular set of physiologic circumstances may reflect a considerable number of contributory physiologic factors[1] In addition to "therapeutic edema produced by the infusion of sodium chloride solution (as in burn therapy) the following types may be considered (1) nutritional, (2) hypostatic, (3) cardiac, (4) renal, (5) hepatic, (6) hormonal, (7) lymphedema, (8) lipedema, and (9) allergic and inflammatory edema

Nutritional (starvation) edema The classic concept was that the edema which frequently is observed in starved populations was the result of a simple depletion of body protein with attendant depletion of the plasma proteins themselves and, in particular albumin (Fig 24) Yet this concept has been questioned by Keys and his associates[29] following a prolonged study of 34 normal male volunteers in whom famine edema was produced experimentally (Fig. 29) These men lost approximately a quarter of their body weight, the ratio of extracellular water to cellular tissue was roughly doubled and their clinical state resembled that seen in Europe among prisoners of war during 1945 There were no signs of renal or cardiac failure and the plasma protein concentration fell only slightly, with the albumin globulin (A G) ratio remaining within normal limits The venous pressure was found to be about 50 per cent below normal Keys and his co-workers concluded that obviously a lowered serum albumin level *per se* could not be the explanation

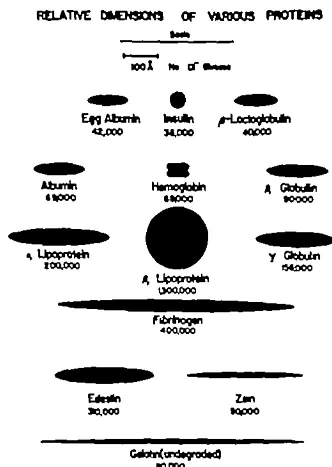


Fig 24 Mere physical size limits the transcapillary movement of many molecules. (From ARMSTRONG S H In *Physiologic Principles of Surgery* edited by L. M Zimmerman and R. Levine Philadelphia and London, W B Saunders Company 1957 Based on data of Oncley J L Scatchard G., and Brown A Physical-chemical characteristics of certain of the proteins of normal human plasma J Physiol & Colloid Chem 51: 181 1947)

for the observed edema, since the observed albumin level was usually within normal limits.

Therefore, while in many starved subjects hypoproteinemia does occur in conjunction with the formation of edema the edema need not necessarily be the result of the diminished plasma protein level

More recently, Berkman[4] has advanced a concept of starvation edema which rests upon the apparent demonstration that the kidney of the starved individual is less able to excrete sodium than is the kidney of the same individual in health In treating patients with anorexia nervosa, he found that most of these individuals would develop clinical edema if in therapy sodium were given in excess of the limited ability

of the "starved" kidney to excrete this ion However, if in therapeutic alimentation the amount of sodium in the diet were limited strictly to the amount which the particular patient could excrete, then edema did not develop no matter how much water was given in the diet Moreover, when the patient had regained health, there was a progressive increase in the ability to excrete sodium until an essentially normal rate for sodium excretion had been reached This additional evidence would appear to fit in with that presented by Keys and his group to the effect that famine edema is not due simply to a diminished colloid-osmotic pressure of plasma resulting from a diminished level of circulating plasma protein but may, in fact, represent still another instance of renal inability to excrete sodium in a normal manner

Hypostatic ("physiologic") edema Before discussing additional types of edema, perhaps it should be recalled that many normal individuals will develop pitting edema of the ankles if the legs are held continuously in a dependent position for a number of hours without exercise. For example, during World War II the writer attended the removal of approximately 500 healthy young German soldiers from Newport News, Virginia, to Rupert, Idaho, on a prisoner-of-war train These troops represented the cream of Rommel's Afrika Korps and were in splendid physical condition Nevertheless, after sitting upright under armed guard for four consecutive days (they might neither stand nor lie down, and only one man in each car might go to the latrine at a time) these men exhibited a 12 per cent incidence of varying degrees of pitting edema of the ankles

Regarding hydrostatic venous pressure and dependent edema, certain of the studies reported by Wood[57] are of interest To review briefly, the generally accepted theory is that fluid transfer across the capillary membrane is regulated, as originally hypothesized by Starling and measured by Landis, by the balance between the hydrostatic pressure which tends to force fluid from the capillaries and the colloidal osmotic pressure of the plasma which tends to draw fluid back into the capillaries (Fig 17) The hydrostatic pressure at the *arterial* end of the capillary has been shown to be approximately 32 mm Hg and at the venous end approximately half of this value; in contrast, the colloidal osmotic pressure of the plasma protein is approximately 25 mm Hg, being somewhat greater, through hemoconcentration, at the venous end than at the arterial end of the capillary If capillary hydrostatic pressure at the *venous* end of the capillary increases to values above 30 mm Hg (that is, to levels above the colloidal osmotic pressure exerted by the plasma proteins) more fluid is lost through the capillary walls and edema formation occurs, when a person stands quietly in the erect position, the venous pressure may rise to levels several times greater than the colloidal osmotic pressure of the plasma

Wood and his associates estimated that during standing and walking for 10 minutes the rate of fluid loss from the vessels into the tissues is approximately 20 cc per minute, representing a loss of 200 cc of fluid from the blood during this 10-minute period It is apparent that such losses could not continue indefinitely without producing serious circulatory alterations and a fall in blood pressure, were the losses into the tissues sufficiently great In this connection, it has long been observed that if a formation of soldiers is made to stand at rigid attention for a prolonged period some of the group may faint, particularly if the unit has not been rigidly conditioned physically This doubtless reflects both a loss of fluid into the tissues of the lower extremities and, perhaps also, a certain vasomotor instability, the latter has been shown to be improved on exercise and conditioning, and to be aggravated by prolonged illness or bed rest

Fortunately, there are a number of processes which tend to reverse the flow of water into the tissues on prolonged standing

One of the more important of these mechanisms is the maintenance of tone by the skeletal muscles, and this is particularly improved by walking When an individual at rest in the upright position takes a step, there is a prompt increase in venous pressure followed by a rapid decrease in venous pressure and then, if the stationary upright position is regained, there is a gradual rise of venous pressure at the ankle to the level which was present before the step was taken The contraction of the voluntary muscles propels the column of blood towards the heart, and the valves of the larger veins prevent backflow of the blood which was extruded from the extremity Even during walking however, the mean venous pressure is approximately 30 mm. Hg the threshold for edema formation[57] Mechanisms other than the pump mechanism of the voluntary muscles are, first an increase in the tissue pressure of the extremity as fluid is lost from the vessels, which tends to diminish the rate of fluid loss from the vessels into the tissues and to encourage the flow of water from the tissues back into the capillaries Second, there is an increased flow of lymph into the venous capillaries or along the lymphatic channels to empty into the thoracic duct. This increases the return of fluid from the lower leg. There are doubtless other factors which are unknown at the present time

Edema of venous origin is essentially hypostatic in nature Edema of the lower leg frequently occurs in various types of venous disease that are associated with an increase in *peripheral venous pressure* in contradistinction to *central venous pressure* which is increased in heart failure The edema of the ankle that is associated with incompetent valves of the great saphenous vein and its tributaries represents a common example of an increase in venous pressure A second example of venous edema is that which is found in association with an arteriovenous fistula where the arterial pressure is transmitted directly into the venous system with a consequent transudation of fluid

Hydrostatic edema of the legs may be caused also by the pressure of massive ascites upon the inferior vena cava We once measured femoral venous pressure continuously during paracentesis in such a patient, and the pressure was observed to fall gradually from an initially much elevated level to a normal level at the completion of the tap During the next 48 hours the leg edema subsided

Cardiac edema Despite the controversy which has been going on for a number of years regarding the causes and the mechanism of the clinical complex termed heart failure, most workers appear to have returned to the fundamental concept that the manifestations of heart failure are basically due to failure of the heart regardless of what secondary phenomena may occur Moreover, the signs and symptoms of heart failure in the individual patient appear to be the result of a cardiac output that is inadequate for the patient in question at a given time, regardless of the absolute volume

Other considerations aside, many observers feel that cardiac edema results, at least in part, from inadequate renal excretion of sodium with consequent retention of sodium and (with it) water in the tissues The absolute increase in the volume of the circulating blood that results from salt and water retention increases, in turn, the venous return to the right side of the heart However, since cardiac propulsion of blood is inefficient a damming back of blood entering the right atrium results in a rise in venous pressure with the resulting extensive hydrostatic effect in the venous capillary bed, an increase in the flow of fluid out of the vascular system produces clinical edema. Therefore sodium retention and an increased venous pressure (in part due to the retained sodium and water) would appear to be factors which induce cardiac edema. An important diagnostic point to be used in differentiating pitting edema of the extremities due to heart failure *is that if the* pitting edema of the extremities has not

been associated with dyspnea, the edema is probably not due to heart failure[47] In other words, to confirm a diagnosis of cardiac edema of the lower extremities or elsewhere one should demonstrate collateral evidence of heart failure At first the edema of heart failure, as is other edema due to increased venous pressure, is noted only near the end of the day or on prolonged standing, but later this edema may be generalized to the extent of anasarca Classically, cardiac edema is dependent edema, and the presacral area of the bed patient should be examined for pitting when cardiac edema is suspected In contrast to the venous edema due to obstruction of the veins of an extremity, cardiac edema is associated with an elevation of both the peripheral venous pressure *and* the central venous pressure

Pulmonary edema, common in heart failure of certain types, is precipitated when the capillary hydrostatic pressure exceeds the level of colloid osmotic pressure and other forces tending to return fluid in the alveoli to the blood stream Positive pressure breathing is helpful (p 386)

Renal edema One of the striking clinical examples of edema formation is that observed in nephrosis or in acute or chronic nephritis Edema in acute nephritis may be due in part to a generalized increase in capillary permeability due to a toxic injury Normally, the renal capillaries are relatively impermeable to protein (Fig 25)

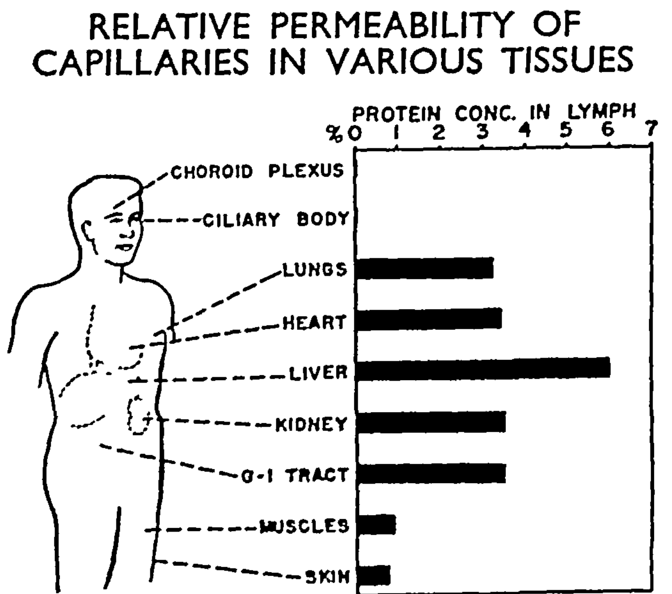


Fig 25 It is now appreciated that the capillaries in certain organs, especially the liver, are normally permeable to protein (From Rushmer, R F *Cardiac Diagnosis A Physiologic Approach* Philadelphia, W B Saunders Company, 1956)

In nephrosis, however, it has been repeatedly demonstrated that there is a marked loss of albumin in the urine and that the plasma proteins which remain in the blood vessels to provide colloidal osmotic pressure are qualitatively different from normal In general, the serum albumin level closely parallels the degree of edema in nephrosis, though diuresis may occur when there has been relatively little increase in the serum albumin level[47] Yet, the loss of proteins in the urine in nephrosis is only one part of the complex picture of this disease, for it has long been appreciated that the processes of serum protein formation may be abnormal in nephrosis

The basal metabolic rate has frequently been recorded as depressed in nephrosis and the possibility of a myxedematous element advanced Nevertheless, the significance of individual studies has often been impaired by the fact that the measured metabolic rates were not correlated with the lean body mass Obviously, massive edema cannot be considered as representing metabolically active tissue

Hepatic edema The leg edema and the ascites which appear in many cases of portal cirrhosis may serve as examples of hepatic edema There has been and there remains a considerable lack of precise information regarding the factors which produce edema in the presence of hepatic cirrhosis, but at least two factors are generally agreed upon and a third is debated First, there is the *increased hydrostatic pressure* in the portal venous system, due to obstruction of portal blood flow through the liver as a result of the generalized fibrosis and regeneration The normal portal venous pressure is approximately 100 mm of water (8 mm Hg), but we do not commonly consider that it is pathologically elevated until the level is

above 200 mm (Fig 74) Second, the liver is the site of the formation of the *plasma proteins* (Fig 73), which supply the highly important intravascular increment of colloid osmotic pressure The plasma protein levels are often diminished in the presence of liver disease. This is especially true of albumin and it is this protein that, because of its smaller molecule and hence greater number of dispersed particles (gram for gram, as compared with globulin), is chiefly responsible for the colloid osmotic pressure of the plasma. Again, it is the number of particles in solution, rather than the size of the particles, that is important in terms of osmotic pressure exerted Third, there has been evidence, though questioned by some, that the diseased liver is unable rapidly to inactivate the posterior pituitary *antidiuretic hormone* Others have suggested that perhaps the metabolism of the posterior pituitary antidiuretic hormone (ADH) is normal in liver disease but that the metabolism of adrenocortical steroids by the liver is abnormal, and that since the antidiuretic hormone and the adrenal steroids are in many respects antagonists in water metabolism the unopposed action of the posterior pituitary antidiuretic hormone results in water retention through an increased renal tubular reabsorption of water Fourth, there is evidence that sodium is retained in the presence of portal cirrhosis There can be little doubt that there does exist a relationship between hepatic and renal function in a number of conditions such as acute hepatic failure, following operation ("hepatorenal syndrome"), irreversible shock and essential hypertension Endocrine factors may well be important in producing sodium retention.

Hormonal edema Various hormonal influences may result in edema as has been seen The adrenocortical steroids probably produce edema by limiting sodium excretion through increasing renal tubular reabsorption of this ion The most striking of these hormones is *desoxycorticosterone,* which results in a retention of sodium, chloride and water and an excretion of potassium. *Aldosterone* has a similar effect. The administration of *cortisone* or *hydrocortisone* may produce edema, as may the administration of *testosterone* in some individuals *Estrogens* notoriously may cause retention of water, premenstrual tension being an example The absence of an adequate amount of *thyroid hormone* results in the characteristic extravascular deposits of water and protein known as myxedema, and thyroid substitution therapy effects dramatic mobilization of these collections The etiology of eclampsia of pregnancy is not entirely clear, but there can be little doubt that endocrine factors play a major rôle Excessive amounts of *pitressin* might result in edema formation

Lymphedema Edema may result from inadequacy of the lymphatic drainage of an affected extremity The most common example seen in surgery is the lymphedema which develops in the arm on the involved side following radical mastectomy with extensive excision of the axillary lymph nodes and lymphatics However, defective lymphatic drainage may also result from inflammatory or neoplastic occlusion of the lymph channels and nodes draining an extremity, or it may be due to a congenital defect in the lymphatic system as seen in congenital lymphedema

The *treatment* of massive lymphedema of an extremity is usually rather unsatisfactory When the condition involves the lower extremity, the Kondoleon operation may be employed. This consists of excising the subcutaneous tissues down to the fascia overlying the leg muscles, one-half the circumference of the leg is treated at the first operation and the other one-half at a later stage To excise the subcutaneous tissue of the entire circumference of the leg at one operation incurs the unnecessary risk of a massive slough of the undermined skin However, some surgeons prefer to excise the skin as well and to graft with split thickness skin grafts taken from the upper thighs, the abdomen or the back. Even so, the operation

is palliative and the results are often disappointing

The lymphedema of the arm which follows radical mastectomy can be exceedingly unsightly and can cause marked psychic trauma Treatment for this condition has not been particularly satisfactory, though certain measures do improve it First, the patient should sleep with this arm elevated on a pillow, if possible, and it is helpful to apply an elastic bandage from the fingers upward towards the shoulder during the night Second, it has been observed that exposure of the involved extremity to sunlight often results in inflammation and further swelling, and thus excessive exposure of the extremity to sunlight should be avoided Third, the injection of hyaluronidase may improve lymph drainage Finally, the Kondoleon operation has also been used upon the arm, but we do not advocate it

Lipedema This is a condition observed almost entirely in women in which fat with a large water content is deposited, usually symmetrically, around the buttocks, thighs, and even the legs but not including the feet. This fat is often tender and hypersensitive Hines[28] believes that the condition is probably due to the effects of gravity on the circulation in a tissue that constitutes a poor supporting structure and which consequently offers little resistance to the passage of fluid from the blood and lymph vessels into the surrounding tissue spaces To be sure, hormonal factors have a bearing here, if for no other reason than that the hormonal factors cause the specific distribution of the female fat

As a striking example of estrogen effect on fat deposition, let me cite a girl in her early teens who had the adrenogenital syndrome (Fig 251) She was placed on oral cortisone therapy to suppress the adrenal production of androgens and this was successful, as reflected in a fall of the urinary 17-ketosteroids to normal This permitted feminization by her own estrogens and the process proceeded at a rapid rate. Unfortunately, the fat deposited in the buttocks and thighs was asymmetrically distributed and her complaint now was that one thigh and buttock were considerably larger than their opposites However, this asymmetry disappeared during the next few months, when the fat deposition in the second thigh achieved symmetry with that of the first in forming the usual female contours

Allergic edema This condition is commonly observed in the swelling of the lips, periorbital tissues and face in the syndrome referred to as angioneurotic edema A similar phenomenon is of course associated with the familiar urticaria or hives or with the histamine flare and surrounding wheal. This is probably due to vasodilatation with an accompanying inflammatory process which temporarily increases capillary permeability

Inflammatory edema is present in, beneath, and surrounding almost all wounds and injuries, and is an integral part of the inflammatory process

It will be clear that body fluid distribution is regulated by many different forces, among these being hydrostatic pressure, osmolar forces, and hormonal influences

Membrane Transfer

Only the briefest mention has been accorded the processes by which molecules pass through the walls of the capillaries—which anatomically consist of supposedly closed spaces but which physiologically obviously do not Too, little has been said regarding the general principles of the transport of substances across other biologic membranes such as tissue cell membranes Though a considerable amount of information has been gathered in these fields, it is not yet possible to present a concise survey which would have obvious clinical applicability at this time Nevertheless, two timely reviews have not only summarized much present information, but they have also afforded a bibliography which may be consulted by those interested in further exploration of the field Pappenheimer[47] surveyed factors influencing the passage of

molecules through capillary walls, and Ussing[35] briefly summarized a portion of the information available concerning transport across biologic membranes

Plasma Sodium Levels: Normal, Low, and High

Although a measurement of the plasma sodium level cannot always be obtained immediately on admission (particularly at night when the technician who operates the flame photometer is absent), a knowledge of this value is most helpful in planning corrective fluid therapy It has been emphasized that the composition of the extracellular fluid—volumetric and electrolytic—is dependent upon its sodium content The amount of sodium ion determines largely, the volume of water to be "held" in the extracellular space, and it is also the principal electrolyte which determines acid base balance, since most of the alkali reserve is in the form of sodium bicarbonate. Therefore, while in most patients satisfactory fluid therapy can be achieved by using plasma "CO_2" and chloride values in the occasional case plasma sodium measurements are almost essential for precise therapy—and sodium values are always useful if available

THE NORMAL PLASMA SODIUM LEVEL. A rule of thumb which is ordinarily valid is that the plasma chloride level (normally 103 mEq) plus the plasma "CO_2" level (normally 27 mEq) plus 12 equals the plasma sodium level ($103 + 27 + 12 = 142$) However this would not be the case in diabetic acidosis or in renal acidosis, since in these instances the kidney, to compensate for the retention of organic (*e g* fatty) acids or inorganic (phosphates, sulfates) acid radicals would have excreted some chloride, hence, the sodium in the left column of the ionic diagram (Fig. 19) would actually be in combination with some bicarbonate, some chloride, and an abnormal amount of one of the organic or inorganic radicals such as acetoacetic acid or sulfates and phosphates Here, then, "CO_2 + chlorides + 12" would not necessarily reflect accurately the plasma sodium level it must be measured. It is obvious that a knowledge of the plasma sodium level is helpful in estimating the osmolarity of the extracellular fluid Again, whereas the milliequivalents of chloride plus the milliequivalents of "CO_2" should ordinarily equal 130, if this value were only 120 in the presence of acidosis it would not necessarily mean that the extracellular fluid was hypotonic, since the difference between 120 and 130 might have been made up by an excess of acid radicals from metabolic sources (Fig 19)

THE LOW SODIUM SYNDROMES[39] A low plasma sodium level has been observed to occur consistently in certain conditions, and these have come to be known as *low sodium syndromes* (Table 2) In surgery, a common example is the low plasma sodium level which is seen following massive trauma, and it does not usually indicate that the absolute quantity of sodium in the body is reduced. Whether this low sodium level is due to an absolute increase in the extracellular fluid volume with consequent dilution of the sodium contained therein, or whether the extracellular volume remains relatively unchanged while sodium migrates into cells or bone, has never been settled to this writer's satisfaction Nevertheless it is a fact that in many patients following major operation the plasma sodium level does fall, and that this change does not need to be treated

A low plasma sodium level may be due to an absolute increase in the extracellular fluid volume while the sodium content remains the same, as just seen. This circumstance may readily lead to the signs and symptoms of water intoxication, and it has been noted particularly in patients with heart failure who have been placed on a prolonged low sodium diet (over many weeks) with unlimited water intake Of distinct importance have been recent reports which indicate that the excess water present in these patients can be mobilized and eliminated by the infusion of alcohol[14] or mannitol[22] A low plasma sodium level may be observed in cirrhosis and in thermal burns, but of

TABLE 2 ETIOLOGY OF ABNORMAL PLASMA SODIUM LEVELS AND BODY SODIUM CONTENT

- I Low sodium syndromes
  - A Absolute sodium deficiency
    1. Inadequate intake—as in low salt diet used in patients with heart failure, or where nonelectrolyte containing fluids are used for prolonged intravenous maintenance
    2. Excessive loss—as in diarrhea, external biliary fistula, ileostomy, gastrointestinal suction, or adrenocortical failure
  - B Water excess—where the normal amount of sodium is present but water logging has occurred, as following mitral valvulotomy.
  - C Following trauma—where no sodium has actually been lost from the body, though the absolute volume of the extracellular fluid may have increased to dilute the sodium present
  - D In cirrhosis—the condition also occurs in some poorly understood circumstances, as in liver disease with or without ascites
- II High sodium syndromes
  - A Hypernatremia and hyperchloremia due to water deficit (perhaps the most common cause)
  - B Hypernatremia and hyperchloremia due to qualitative renal tubular dysfunction We have encountered this condition in patients with various diseases, often following shock Some observers have suggested that the hypernatremia was due to brain damage, but in our cases brain damage was minimal or absent An endocrine factor may be important
- III Sequestration of sodium in "third spaces"
  - A Massive pleural effusion
  - B Rapid ascites
  - C Retroperitoneal effusion in trauma
  - D Fluid in the obstructed bowel
  - E Wound edema
  - F Translocation of sodium following hypodermoclysis with salt-free solution

forts to correct these values by salt therapy are usually ineffective, at least initially

Of course, an actual sodium deficit may account for the low plasma sodium level in patients who through vomiting have lost relatively more salt than water, who have been maintained on intravenous fluids which have not contained adequate amounts of salt, or who have been maintained on a low salt diet Specifically, a low plasma sodium level is often encountered in patients with pyloric obstruction, small bowel obstruction, in certain forms of diarrhea, in the salt-losing nephritis, or occasionally during recovery from renal shut-down. A low plasma sodium level may also be due to adrenocortical insufficiency (Fig 245)

The *treatment of a low plasma sodium level* will depend upon whether absolute sodium deficiency exists, whether absolute water excess is present, or whether the plasma sodium level is in fact "physiologic" following major trauma The treatment of absolute sodium deficiency consists of giving salt-containing fluids, perhaps as 3 per cent sodium chloride solution. The treatment of water excess would formerly have consisted of balancing the water excess with a sodium infusion, but the recent studies cited above indicate that relatively pure water diuresis may be achieved under circumstances of water excess by the administration of either alcohol or mannitol and perhaps urea. Clearly, it is more desirable to remove the water excess than to balance a water excess by producing a proportionate salt excess Finally, in the light of present knowledge, the low sodium level which is observed following massive trauma requires no specific therapy

In patients who present no obvious cause for an observed low plasma sodium level, the possibility of chronic adrenocortical failure should be considered

Elevated plasma sodium levels were discussed previously This circumstance may result from a relative water deficiency (Fig 23), but a qualitative defect in renal tubular function cannot always be excluded (Fig. 60)

The "Third Space" Concept

The term "third space" has appeared with increasing frequency in the recent literature Actually, this is but another phrase to designate fluid that is in neither the intracellular nor the interstitial space, as usually con-

sidered Examples of such fluid translocations are wound edema, ascites, pleural effusion, and losses into the bowel in intestinal obstruction The clinical recognition of such collections is not new, but the term "third space" does emphasize that these deposits of fluid are not as readily available to the interstitial and intracellular spaces and the plasma volume as is normally the case[46] That is, since these collections of fluid cannot be reclaimed by the blood stream with normal facility to replenish the extracellular fluid volume, they must not be depended upon as immediate sources of additional fluid in the treatment of the acutely ill patient Fluid lost into the bowel in intestinal obstruction is not readily reabsorbed, due to the fact that the wall of the involved bowel does not absorb with normal efficiency It has been found that injected substances such as inulin which are used to measure the extracellular volume do not enter such collections of fluid as readily as they do the usual confines of the extracellular space. Therefore, it is not surprising that the physiologic potentialities of these sequestrated bodies of fluid are different from those of the interstitial fluid

Potassium Metabolism and the Correction of Potassium Deficits

GENERAL PHYSIOLOGY Potassium is the principal intracellular cation and its concentration within the cell is more than 25 times that in the extracellular fluid (normal level, 3.5 to 5.5 mEq per L) However the potassium inside the cell is not all in ionized form and does not all exert the same osmotic potential as it would were the entire intracellular potassium content fully ionized. The concentration of potassium within the cell is dependent upon the concentration of potassium outside the cell the pH of the intracellular and the extracellular fluid and the metabolism within the cell at the time When the acidity outside the cell is increased, potassium emerges to neutralize the acid, thus maintaining acid base balance between the tissue cells and perfusate. Using radioisotopes of potassium, it has been found that in the normal person weighing approximately 70 kg the exchangeable potassium ranges from 3000 to 4000 mEq, of which only approximately 75 mEq are in the extracellular fluid. Normally, from 40 to 100 mEq of potassium are excreted in the urine each day, depending, of course, upon the intake, the average excretion is in the range of 50 mEq Therefore, 6 gm. of potassium chloride, which contain approximately 80 mEq of potassium, are more than adequate to cover the daily loss in the urine under normal conditions

POTASSIUM INTOXICATION When the extracellular potassium level rises above 7 mEq per L. there is serious danger of cardiac arrest in diastole and, indeed, the injection of potassium into the aorta proximal to a clamp placed distal to the coronary ostia has been used to stop ventricular fibrillation at operation The injection of potassium usually results in cessation of the fibrillation with the heart stopping in diastole This cation is also used as a cardioplegic agent in open heart surgery

Under conditions of rapid tissue breakdown and oliguria, as are present in acute renal shutdown associated with fever and starvation, the amounts of potassium released from cells can prove lethal if not successfully treated.

Miscellaneous Potassium Effects

FAMILIAL PERIODIC PARALYSIS The relationship which exists between the integrity of normal neuromuscular irritability and muscular tone is well exemplified by examining the relationship between potassium concentration in the extracellular fluid and a peculiar condition involving skeletal muscle familial periodic paralysis This syndrome of muscular weakness is associated with a fall in the plasma potassium level though the onset of attacks is not preceded or accompanied by an increase in the loss of potassium from the body Evidence has been obtained by several groups that the paralysis is associated with a transfer of extra

cellular potassium into the intracellular phase, and they have ascribed this transfer to the cycle of carbohydrate combustion in skeletal muscle During the paralytic seizure or immediately prior to its onset, the plasma potassium values may vary from 2 6 to 3 0 mEq /L (normal, 3 5 to 5 5) The precise cause of the shift of potassium into the cells in these patients is not always clear, but it is known that the administration of insulin or a high carbohydrate intake is prone to increase glycogen formation and thus lower the plasma potassium level and, in susceptible individuals, to produce typical attacks of the paralysis The treatment of the acute attack consists of the intravenous administration of potassium chloride Subsequent episodes can usually be minimized by the consumption of a diet low in carbohydrate, high in protein, and medium in fat

Recently, Conn and his associates[11] have reported an increase in the secretion of aldosterone during attacks of familial paralysis

POTASSIUM AND CARBOHYDRATE METABOLISM[20] The fact that the formation of glycogen within the cell results in a movement of potassium from the extracellular to the intracellular fluid compartment has been used in the medical therapy of impending potassium intoxication (p 79), glucose and insulin being administered for this purpose Since potassium is required for normal glycogen deposition, it has been found that in states of marked potassium deficiency there may intervene almost total absence of liver and muscle glycogen, with the development of a "diabetic" type of glucose tolerance curve In this same connection, it has been observed clinically that patients suffering from postoperative potassium deficiency may develop a gradually increasing glycosuria, the degree of glycosuria bearing a direct relationship to the severity of the intracellular potassium deficit

POTASSIUM AND PROTEIN FORMATION In the fasting mammal, potassium and nitrogen are excreted in the urine in the ratio of approximately 1 10 It is therefore possible to gain some knowledge of the nitrogen balance when the potassium balance is known This is because these elements exist in lean tissue in the proportions given In 1951 Cannon and his associates[10] reported their investigations concerning the relationship which exists between nitrogen storage and available potassium They found that rats given potassium chloride in addition to the basal ration, which was deficient in potassium, grew at a greater rate than did the controls, who received no potassium supplement Moreover, the animals that had received potassium had better appetites and consequently ingested greater amounts of food, an effect which we have observed in dogs[24] Subsequent reports have confirmed that in both animals and human beings potassium must be available for normal protein formation

POTASSIUM AND THE HEART EFFECTS OF OTHER IONS The influence of potassium upon normal myocardial function is reflected in the fact that consistent changes appear in the electrocardiogram (ECG) in states of potassium deficiency, and that elevated potassium concentrations produce cardiac arrest The ECG (Fig 142) alterations consist of a diminished voltage, flattening and eventual inversion of the T-wave, and prolongation of the Q-T interval However, these changes can be altered by the administration of other ions, for the electrical activity of the heart reflects both total and relative ionic effects For example, the deleterious effects of an elevated plasma potassium level upon the heart can be diminished by the infusion of sodium chloride, and, in fact, there is considerable biochemical evidence to indicate a reciprocal physiologic relationship between potassium and sodium under a variety of circumstances For instance, during potassium depletion the sodium content of cardiac and skeletal muscle increases, and in states of potassium deficiency the administration of excessive amounts of sodium ion may further aggravate the condition The administration of

only sodium ion in metabolic alkalosis due to potassium depletion can further increase the gravity of the situation, in rats, the administration of a high sodium low potassium intake during protein repletion, following potassium and protein depletion, was shown by Cannon and co workers[9] to result in congestive heart failure and pulmonary edema, associated with a characteristic type of myocardial necrosis

RELATIONSHIP BETWEEN POTASSIUM DEFICIENCY AND METABOLIC ALKALOSIS Darrow and his associates[15, 16] published searching studies regarding the relationship which appears to exist between potassium deficiency and metabolic alkalosis In brief, they showed that there is a reciprocal correlation between intracellular potassium and cellular sodium content, and they calculated that as much as one-half of an intracellular potassium deficit may be replaced by about two thirds of the equivalent amount of sodium, the additional potassium being replaced by hydrogen ion. Muscle analyses showed that in alkalosis the cellular concentration of potassium was decreased. Moreover, high plasma bicarbonate and low plasma chloride levels almost invariably accompanied the low muscle potassium and the high muscle sodium levels—regardless of whether the potassium deficiency had been produced by potassium losses such as occurred in pyloric obstruction by low potassium diets, desoxycorticosterone therapy, or the prolonged administration of sodium salts in the presence of a low potassium diet Further clarifying this problem Darrow and his co-workers showed that the administration of potassium chloride in the presence of metabolic alkalosis due to cellular potassium deficiency resulted in a movement of the administered potassium ion into the cell and a movement of sodium and hydrogen ions out of the cell The movement of the acid hydrogen ion out of the cell reduced the sodium bicarbonate level in the extracellular fluid Moreover, as the hydrogen ion was excreted by the kidney while sodium ion was being conserved, there resulted the apparent paradox of an acid urine during the recovery period, even in the presence of metabolic alkalosis

Burnell and Scribner[8] subsequently published data which partially reopened the question of whether the alkalosis (as in pyloric obstruction) is the *result* or the *cause* of the lowered plasma potassium level In brief, they showed that by infusing alkali the plasma potassium level could regularly be lowered and by infusing acid it could be raised—this in the nephrectomized animal We and others have confirmed these findings (though the amount of acid that must be infused to produce a significant change exceeds physiologic limits), and thus the precise role of potassium metabolism in the genesis of alkalosis must await further study

Clinical Potassium Deficiency

ETIOLOGY AND DIAGNOSIS Potassium deficiency is to be anticipated in the same clinical situations that are found to have resulted in deficits of water and other electrolytes Among these are pyloric or intestinal obstruction with vomiting diarrhea, small bowel fistulas, an ileostomy, the more chronic stages of burn injuries, diabetic acidosis, prolonged gastrointestinal suction without adequate replacement of potassium, ACTH or cortisone therapy without adequate potassium supplementation or prolonged parenteral maintenance of the patient with solutions which contain little potassium Since most foods contain considerable amounts of potassium, especially meat, it is rare indeed for potassium deficiency to develop in a normal individual who is eating a normal diet. By the same token once a patient is taking food again by mouth the diet can usually be depended upon to supply an adequate potassium intake though an existing deficit can be more rapidly overcome by providing oral supplements in the form of potassium chloride

The diagnosis of a probable cellular potassium deficit is best established by measuring the plasma potassium level and find-

ing it low. Of course, Scribner's work suggests that if alkalosis is present a low plasma potassium level may not necessarily indicate a cellular deficit, though a deficit will usually be present. Moreover, the plasma potassium level may be normal on admission only to decline following hydration of the patient; for this reason, the level should be rechecked from time to time. The ECG is useful in following the net cardiac effects of hypokalemia and hyperkalemia, but it does not afford quantitative information regarding the plasma potassium level.

Finally, the conclusive proof of a potassium deficit in the given patient is provided by a balance study which demonstrates the retention of significant amounts of administered potassium.

CLINICAL FINDINGS IN POTASSIUM DEFICIENCY. The *symptoms and signs* of potassium deficiency, as with various of the other electrolyte deficiencies, are not very specific. A feeling of weakness or listlessness is not uncommon, and a loss of appetite has been reported both in human beings and in experimental animals. Postoperative gastrointestinal distention may be due to potassium deficiency, though perhaps not quite so often as has been indicated in the literature. Severe potassium deficiency, however, can result in profound muscular weakness, disorientation, and even coma.

TREATMENT OF POTASSIUM DEFICITS: FURTHER COMMENT. Prophylactic measures are important in preventing the development of a potassium deficiency, for the kidney cannot conserve potassium with the efficiency with which it can conserve sodium and chloride. That is, there is an obligatory excretion by the renal tubules of some potassium, regardless of how low the plasma level or how great the intracellular deficit. Therefore, it is important to provide parenteral potassium intake in a patient who cannot ingest food over a prolonged period of time. Prophylactic amounts of potassium should also be administered parenterally in the presence of intestinal disease (vomiting, diarrhea, or fistula), or when adrenal steroids or ACTH are given.

The replacement of existing potassium deficits is, in our practice, usually achieved by the infusion of potassium chloride. Six grams of potassium chloride placed in a liter of almost any type of fluid that is to be given (representing a 0.6 per cent solution) provides approximately 80 mEq. of potassium. Since the daily excretion of potassium in health is approximately 50 mEq. in the urine, the administration of 6 gm. of potassium chloride (13.4 mEq. of K per gm.) does little more than cover the daily requirements, without significantly reducing the deficit. Accordingly, when a significant potassium deficit exists we usually give 6 gm. of potassium chloride in each of 2 L. of fluid, given at separate times of the day. For example, if the patient is to receive 3 L. of fluid, the first liter would contain 6 gm. of potassium chloride, given over a period of not less than 2 hours, and the last liter would also contain 6 gm. of this salt. This may be given in 0.4 per cent sodium chloride or in glucose solution or in one of the protein hydrolysates.

A *practical precaution* to be employed in potassium therapy is that renal function must be adequate in the individual to avoid the production of an excessive plasma potassium level, since 6 gm. of potassium chloride represents an amount of potassium ion equal to that normally found in the entire extracellular space. The rate of infusion must permit cellular uptake of the infused ion.

The renal excretion of potassium represents an important protective function, as is quickly apparent in anuria; potassium is liberated by metabolism.

Where the potassium deficit is great, a number of days are usually required to overcome the depletion, even when as much as 12 gm. or more of potassium chloride are administered each day. Using radiopotassium, we found that in the patient with prolonged intestinal obstruction, without adequate potassium replacement, the potassium

pool might be only approximately one-half the normal of perhaps 3000 to 4000 mEq Nevertheless, such a figure may not reflect the clinical picture with complete accuracy, for the individual will have metabolized a considerable number of lean tissue cells In other words, to suddenly provide such a patient with his full pre-illness stores of potassium would result in potassium intoxication, for he no longer has a normal lean tissue mass

A General Approach to Fluid Therapy

Diagnosis of Fluid Imbalance

In this section consideration will be given to the following topics volume deficit, osmolar deficit, specific ion deficits, and acid base status

VOLUME (WATER) DEFICIT When the patient is seen on admission, it is important to estimate the probable volume deficit, that is the volume of fluid that has been lost from the body Clinical experience has shown that when the individual is only mildly dehydrated he has lost from 2 to 4 per cent of his body weight as water If he appears moderately dehydrated this figure is more accurately 4 to 6 per cent and if he is markedly dehydrated he has lost from 8 to 10 per cent In practice we use the figures of 4, 6, and 8 per cent

The actual assessment of the probable volume deficit rests largely on the clinical evaluation of the patient The *history* should include questions regarding recent weight loss fluid intake, urinary output, vomiting diarrhea and other pertinent facts On *physical examination* the condition of the tongue skin turgor eyeballs and cheek pulse rate and blood pressure should be noted. The color of the urine, if quite dark would indicate a diminished urine flow for in health the absolute amount of pigment excreted each 24 hours is almost constant regardless of urine volume. The important point to note is that *the diagnosis of the volume deficit must rest primarily on clinical grounds,* though collateral evidence is derived from laboratory measurement of the concentrations of the blood constituents. The body weight measurement is also helpful in infants, for a rather close check of the weights of babies has often been kept. Once the percentage of weight loss as water has been estimated from the clinical examination, the value is considered as kilograms or liters of fluid required to replace the volume deficit

OSMOLAR (SALT) DEFICIT Having estimated the approximate volume of water that has been lost and hence the approximate volume of water that must be replaced, the next step is to decide what the volume of water is to contain in the way of salts Perhaps no salt is required, at least initially, in which case the therapeutic solution would consist of 5 per cent glucose in water The glucose has two purposes, one to introduce the four calories made available by each gram of the sugar and the other to render the solution more nearly isotonic—for distilled water is hypotonic, it would be irritating, and it would cause red cell hemolysis

However, as noted previously, clinical fluid losses almost invariably represent mixed losses and some salt is usually required in therapy It is therefore important to know relatively how much salt is needed by estimating the *osmolar deficit*, that is whether the remaining extracellular fluid is hypotonic due to inadequate salt content or is hypertonic due to a relatively greater water loss than salt loss Moyer[41, 42] has emphasized a simple rule of thumb which is useful clinically, namely, that normally the sum of the milliequivalents of chloride plus the milliequivalents of carbon dioxide combining power (103 + 27) is equal to approximately 130 mEq/L of extracellular fluid If the sum of the values is greater than 135 mEq/L of extracellular fluid (measured in plasma), then the extracellular fluid is relatively hypertonic (hyperosmolarity), that is, the extracellular fluid remaining to the patient contains relatively more salt than water Here therapy should be initiated

with salt free solutions, such as 5 or 10 per cent glucose in water On the other hand, if the sum of these two values is less than 120 mEq, then the patient requires relatively more salt than water and either isotonic or hypertonic sodium chloride solution should be used to initiate therapy

ACID-BASE STATUS Third, when one has estimated the *volume deficit* by means of the clinical examination of the patient (plus hemoconcentration) and has estimated the *osmolar deficit* by means of the laboratory measurements of plasma chloride and "CO_2" levels, the next step in the diagnosis of the state of fluid imbalance is that of determining whether or not *acid-base imbalance* exists For practical purposes, this is usually done by a clinical estimate of the probable circumstances, used in conjunction with measurements of the carbon dioxide combining power To be sure, an elevated carbon dioxide combining power might represent either compensated respiratory acidosis or metabolic alkalosis (Fig 26) Similarly, a lowered carbon dioxide combining power could signify the presence of either meta-

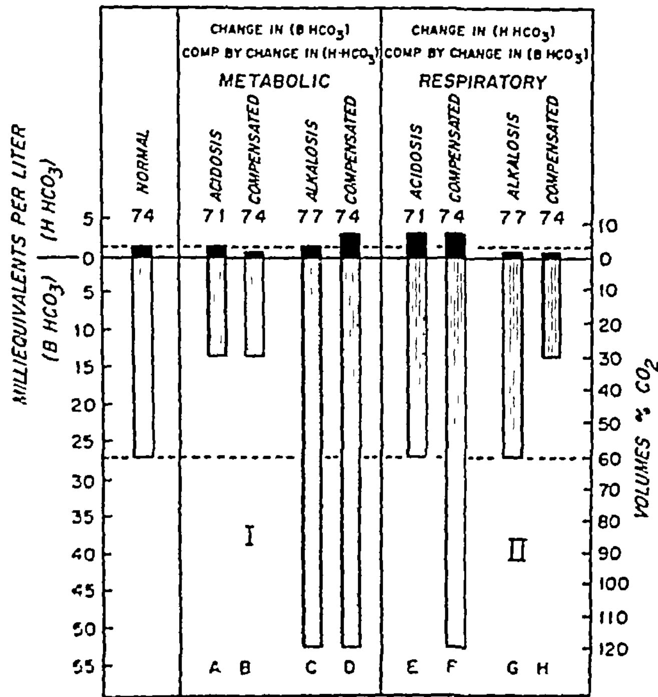


Fig 26 Metabolic acidosis and alkalosis, and respiratory acidosis and alkalosis (Modified from Gamble, J L *Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid*, Cambridge, Mass, Harvard University Press, 1917)

bolic acidosis or respiratory alkalosis sired, the precise reaction of the bloo be determined by measuring the blo moreover, using the blood pH, the blo tent of carbonic acid (or PCO_2), a bon dioxide combining power one scribe accurately the acid-base relati existing in the plasma at the time o urement

Fortunately, these laborious techn not usually essential for practical fluid therapy one estimates from th cal examination the probable pres alkalosis or acidosis, and most of t the degree of either will be adequat flected in the carbon dioxide con power value to permit satisfactory p therapy In the absence of an oppo actually to examine the patient cli the measurements of base-bicarbona bonic acid, and blood pH would all sirable to profile the acid-base relati in the extracellular fluid Even so, as it is neither necessary nor desirable sider the chemistry values apart fr clinical evaluation of the patient contemplation of the diagrams in Fig will clarify understanding of these base relationships

SPECIFIC ION DEFICITS POTASSIUM, CA AND MAGNESIUM A fourth step in th nosis of the state of fluid imbalance the patient in question has (regard how the particular abnormality in flu ance may have been produced in t tient) is that of estimating whether the ions of *potassium, calcium,* and *nesium* are present in adequate am Practically speaking, it is potassium t shall be most concerned with, since th large stores of calcium available bones, and it is only under special c stances (most often, parathyroid defic that inadequate supplies of ionized c are present to preserve normal neur cular irritability Of course, a suffic low serum calcium level results in calcemic tetany

A rapid and accurate method f

measurement of the plasma magnesium level is not yet available and, since at present knowledge concerning the clinical importance of the magnesium ion is scanty, it is rarely given in therapy. Although various types of clinical changes have been attributed to hypomagnesemia and to hypermagnesemia, largely on the basis of animal experiments, it is most uncommon in surgical practice to encounter a patient in whom, first, hypomagnesemia is documented and in whom, second, there are definite symptoms and signs which may be attributed to this deficiency. In general it has been maintained that the clinical signs and symptoms produced by an increased serum level of magnesium appear to be lethargy, which progresses into coma, and respiratory failure. There is evidence that the magnesium level may be elevated in some severely wounded individuals and in shock states.

Hypomagnesemia has been reported to cause cutaneous vasodilatation and hyperexcitability progressing to tetany. The normal level of magnesium in extracellular fluid is from 1.4 to 2.5 mEq. per L., and this level is much higher in the intracellular fluid (Fig. 15). Alterations in the electrocardiogram have been reported in magnesium deficiency, perhaps because of the fact that calcium and magnesium both have an effect upon cardiac neuromuscular irritability.

Specific Pathologic Fluid States in Surgery

Pyloric Obstruction with Vomiting: Mixed Water and Salt Loss with Metabolic Alkalosis

The state of fluid imbalance which results from pyloric obstruction with prolonged vomiting represents perhaps the most important single type of fluid derangement in surgical practice. It is a very common one, a feature which it shares with that due to intestinal obstruction. The profile of the normal plasma chemistry values is shown in Figure 15 and the changes in pyloric obstruction with vomiting are shown in Figure 124. From a knowledge of the electrolyte content of gastric juice, one knows that the patient will have lost large amounts of chloride (perhaps 100 mEq. per L. of gastric juice), some sodium (perhaps 50 mEq. per L.), and from 5 to 15 mEq. of potassium per L. of gastric juice. With these electrolytes he has also lost water, possibly from 2 to 4 L. per day when completely obstructed—a rate of net loss not long tolerated, however.

CASE STUDY. Let us assume that a patient has been admitted to the hospital with a history of prolonged vomiting. The evidence indicates that the site of obstruction is probably at the pylorus. He is known to have had a duodenal ulcer in the past and the vomitus, while brownish, does not contain obvious bile; moreover, roentgenograms of the stomach confirm obstruction at the pylorus.

How much, of what type of fluid, shall be given this 154 lb. (70-kg.) man, and over how many hours?

The *volume deficit* (the amount of fluid to be replaced) should first be estimated by judging the degree of dehydration. The physical findings suggest marked dehydration, or a water loss equal to 8 per cent of body weight. 8 per cent of 70 kg. = 5.6 L.

Second, does an *osmolar (salt) deficit* exist? To decide this point a blood specimen is sent immediately to the laboratory for plasma chloride and carbon dioxide combining power measurements. Treatment is begun with isotonic saline in 5 per cent glucose solution while the laboratory analyses are being performed. The sum of "chlorides plus CO_2" is found to be 112 mEq. per L. It will be recalled that this value should normally be approximately 130 mEq. per L. Thus, one finds that while the patient has lost a large amount of water, he *has* lost even more salt, relatively speaking, and that the extracellular fluid which remains to him is relatively hypotonic. That is, hypo-osmolarity exists and in early therapy fluid should certainly contain salt.

least isotonic concentration, if one does not elect to give an hypertonic sodium chloride solution We usually do give 500 cc of a 3 per cent solution to individuals whose extracellular fluid is hypotonic at the time of admission, continuing thereafter with the remainder of the therapy However, in the vast majority of instances efficiently functioning kidneys may be depended upon to restore normal osmolarity on isotonic saline therapy, without requiring hypertonic saline solution So, all 5 6 L of the volume that is to be given should be *in the form of* isotonic sodium chloride—unless from 500 cc to 1 L is given in the form of a 3 per cent sodium chloride solution Of course, continuing losses during therapy must be added to the deficit initially estimated at 5 6 L, if one is to restore the required volume of body water. In practice, one "rounds out" the 5 6 to 6 L

Third, it is important to estimate the *acid-base status* of this individual The plasma chloride level was reported from the laboratory as 78 mEq per L (normal, 103 mEq) and the plasma carbon dioxide combining power as 34 mEq per L (normal, 27) These values are compatible with either metabolic alkalosis or compensated respiratory acidosis (Fig 26), but on the basis of the obvious vomiting the presence of metabolic alkalosis appears virtually certain—and there is no pulmonary disease to suggest that respiratory acidosis might exist

While there may be some pulmonary compensation for the elevated base-bicarbonate (by retention of carbonic acid), this compensation may not have been sufficiently complete to prevent a shift in the reaction (hydrogen ion concentration) toward the alkaline side—a point that can be settled, if desired, with a blood pH determination, if the normal 20 1 ratio of $BHCO_2/H_2CO_3$ has been maintained, the pH will remain normal, but if the increase in H_2CO_3 retention has not kept pace with the $BHCO_3$ increase, perhaps allowing the ratio to increase to 22 1, then the pH will have become more alkaline Even so, pH measurements are not often used in routine clinical fluid management, nor are they essential. In fact, regardless of whether or not measured pH values have changed in metabolic alkalosis, it is probable that pulmonary compensation is rarely complete and that some shift in the pH has usually occurred.

As for management of the metabolic alkalosis produced by pyloric obstruction with vomiting (the most common cause of this condition in surgical practice), there is usually no need for undue haste in its correction unless signs of alkalotic tetany are present Pyloric obstruction in the adult does not constitute a surgical emergency, and there is time to restore fluid balance in an orderly manner We usually depend upon sodium chloride *therapy to correct the* alkalosis and do not infuse ammonium chloride or hydrochloric acid unless the need is clear A liter of extracellular fluid contains 145 mEq of sodium and 103 mEq of chloride, and the infusion of a liter of 0 85 per cent (isotonic) sodium chloride (145 mEq of Na and 145 mEq of Cl) introduces a "physiologic excess" of 42 mEq of chloride, which *in effect represents the* infusion of 42 mEq of hydrochloric acid Since the patient is to get almost 6 L of isotonic sodium chloride solution, a considerable amount of acid (in the form of excess chloride) will be infused Potassium deficits contribute to the development of metabolic alkalosis and should be corrected

In contrast to adults, infants frequently do require specific therapy for alkalosis to abolish tetany If the alkalosis in any patient is sufficiently severe to cause symptoms, then one may give either M/6 ammonium chloride solution or M/10 hydrochloric acid in isotonic solution intravenously

Fourth, it is necessary to decide whether or not a *potassium* deficit exists, otherwise the acid-base balance might not be readily restored with sodium chloride and glucose solutions alone The plasma potassium level is measured with the flame photometer, and it is found that the value is 3 8 mEq per L. (normal, 3 5 to 5 5 mEq per L) Al-

though the value of 3 8 is barely within normal limits after the patient is hydrated this value may be lower, indicating that a deficit does exist As noted above, alkalosis *per se* has been shown to lower the plasma potassium level somewhat, even when no potassium has been lost from the body, but for our purposes here a low plasma potassium level probably reflects a cellular potassium deficit This deficit should be corrected as soon as renal function has been reestablished with 0 6 per cent potassium chloride solution In severe potassium deficits renal function itself may be improved by potassium administration, but such therapy must be conducted cautiously

A normal plasma level may or may not indicate normal cellular stores of potassium, but a sharply lowered plasma potassium level usually reflects a cellular potassium deficit

IN SUMMARY, it has been determined from the clinical examination that the patient under consideration has an initial volume deficit of 5 6 L of water that he needs relatively more salt than water (extracellular fluid is hypotonic), that metabolic alkalosis exists (high "CO_2 and low chlorides, with vomiting), and that the initial "low normal" plasma potassium value may or may not indicate cellular potassium depletion—certainly potassium therapy may be deferred until renal function is improved with initial fluid replacement and until a subsequent measurement of the plasma potassium level reveals a subnormal value However, a potassium deficit probably does exist, for gastric juice has been vomited, with its relatively high potassium content and the potassium intake has been very small Specifically then, we would begin therapy either with a liter of isotonic saline in 5 per cent glucose solution or with 500 cc of 3 per cent sodium chloride solution, followed by the remainder of the volume deficit in the form of isotonic saline in glucose the latter to provide some calories In general we would give these 6 L of fluid during the first 12 to 24 hours following admission, realizing that additional fluid losses will occur by insensible loss, gastric tube suction, and urinary excretion as time passes—and that these losses must be added to the initial deficit of essentially 6 L to achieve rehydration Even so, one need not be particularly concerned over the continuing losses, they can be replaced in due course The important consideration is to reassess both clinical findings and plasma chemistry values at the end of the initial 6 L of therapy, for it will often be found that the therapy already given has more nearly corrected the requirements than anticipated Above all, it is essential to realize that there are no precise and infallible calculations that can be used to compute, at the time of admission, the entire corrective therapy that the patient will require Knowledge of fluid metabolism being what it is, guides in treatment may be employed but beyond this the effect of prior treatment must be constantly re-evaluated by repeated examination of the patient and measurement of the plasma chemistry values A decrease in the *volume deficit* is reflected in improved skin turgor moisture of the tongue and urinary output *Osmolar* and *acid* base status are reflected in plasma chemistry values, as is that of the potassium stores Should a potassium deficit become apparent on the second or third day, from 3 to 6 gm of potassium chloride may be added to any therapeutic solution, as considered necessary In marked deficits, 6 gm may be given twice daily, each dose being infused over a period of not less than 2 hours—and only in the presence of active renal function

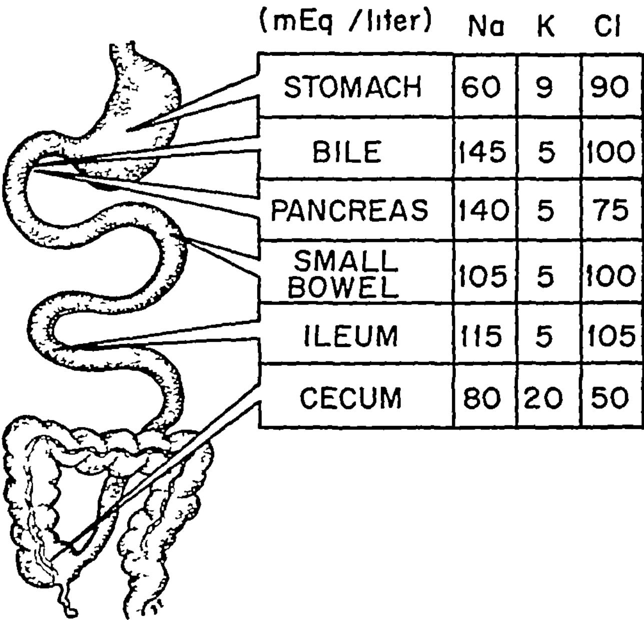
COMMENT The therapy in this case has been outlined in some detail because it presents in an orderly sequence the factors important in establishing an accurate diagnosis of the state of fluid imbalance and in treating the condition found Moreover, the series of steps described and illustrated is applicable to a wide variety of states of fluid imbalance One begins by estimating the *volume* of fluid that needs to be given,

then the *type* of fluid required, whether *acid-base* imbalance is present and, if so, whether or not it needs to be specifically treated with an alkali or an acidifying compound, and, finally, the correction of *potassium* and *calcium* deficits The state of fluid imbalance has often developed over a period of days, and several days are usually required to achieve complete correction

Small Bowel Obstruction

The volume losses in the presence of upper small bowel obstruction may be relatively great, numbering from 6 to 8 L in a single 24-hour period The electrolyte loss is usually a more balanced one than in the presence of pyloric obstruction (where an acid material is lost, producing metabolic alkalosis) or in diarrhea (where relatively more sodium is lost than fixed anions and metabolic acidosis occurs) (Fig 27) Thus, the principal requirement in high small bowel obstruction is usually replacement with a balanced electrolyte solution, such as isotonic sodium chloride solution or, better, a solution of 1 part M/6 sodium bicarbonate and 2 parts isotonic sodium chloride, with adequate amounts of potassium, such a bicarbonate solution more nearly approximates normal plasma values than does isotonic sodium chloride, and it avoids the acidifying effect of a physiologic excess of chloride Of course, one will note whether or not acid-base balance is normal, but marked aberrations in acid-base status are not common findings in uncomplicated small bowel obstruction, if present, they are treated In passing, it should be noted that *in high intestinal obstruction death is most* frequently due to water and salt loss, whereas in low intestinal obstruction death is more often due to loss of integrity of the bowel wall with resulting passage of toxic materials from the bowel lumen into the peritoneal cavity and thence into the blood stream

Only a fraction of the fluid lost into the bowel lumen may be vomited, and thus a relatively large volume of body water may be sequestered in this "third space," unavailable to the dehydrated tissues and circulation but not detectable by the clinician as fluid deficit Accordingly, it is often difficult to estimate, on the basis of weight loss, the precise fluid requirements of the patient with intestinal obstruction, for the fluid sequestered in the bowel still contributes to body weight The writer vividly recalls one patient in whom everything that could be thought of had been done—certainly the amount of fluid that had been infused was considered adequate despite large distended loops of fluid-containing bowel, the result of ileus accompanying peritonitis Nevertheless, the patient's condition was steadily deteriorating and the systolic blood pressure was hovering in the low 90's It was finally decided to give him, quite empirically, an additional 2 L of isotonic sodium chloride solution for want of anything better to do Flame photometers were not available then, and fluid therapy had been conducted solely on the basis of plasma "CO_2" and chloride values Almost miraculously,


ELECTROLYTE CONTENT
OF THE BOWEL AT VARIOUS LEVELS

(mEq/liter)	Na	K	Cl
STOMACH	60	9	90
BILE	145	5	100
PANCREAS	140	5	75
SMALL BOWEL	105	5	100
ILEUM	115	5	105
CECUM	80	20	50

Fig 27 The acid-base derangement produced by vomiting, enteric fistula, or diarrhea is determined by the electrolytes lost (data from RANDALL, H T Water and Electrolyte Balance in Surgery Surg Clin North America, **32:** *445, 1952*)

this increment in saline solution was apparently what was required, the blood pressure promptly rose above 100 and was never at shock levels thereafter It has been pointed out previously that sodium chloride loss is far more apt to produce shock than is the loss of a similar volume of water without salt loss

Since the weight of the individual may not be a reliable guide to the actual extracellular fluid deficit in the patient with intestinal obstruction, here again one must depend upon the blood pressure and pulse rate, urinary volume skin turgor, moisture of the tongue and other usual clinical aids in estimating the volume of fluid that is required—aided of course by the volume of fluid that is aspirated through the Levin or Miller Abbott tube. It should not be forgotten, also, that in addition to the fluid aspirated through the indwelling tube and the urinary volume, one must add an additional fluid supplement, depending upon the climate, to provide for insensible fluid loss

Small Bowel Fistula

As with small bowel obstruction, the fluid loss through a small bowel fistula (Fig. 122) represents a fairly well balanced loss The major problem is to correct the volume deficit and if present, the osmolar deficit marked acid base derangements are uncommon but, if present usually take the form of metabolic acidosis An important feature of the management of a small bowel fistula is that the condition may not be readily remediable by surgical intervention That is not only may from 4 to 8 L of fluid be lost through the fistula in a 24-hour period but one has little knowledge of precisely when the fistula will close Fortunately most small bowel fistulas, including those involving the duodenum, do close over a period of from a few days to a few weeks Nevertheless since one will need to replace perhaps 5 L. of drainage from the fistulous site (collected by catheter suction) 1500 cc of urine and 1 L of insensible fluid loss—a total volume of 7 5 L. in a 24-hour period—it is obvious that the greatest conservation of veins must be achieved, beginning on the very fingers and moving methodically upward Otherwise, the available veins may be quickly occluded by thrombosis, and after one has cut down on the ankle veins and the antecubital veins he may be in a very difficult position from the standpoint of administering fluid to the patient Even so, the outlook in small bowel fistula is far better than it formerly was, since it is possible more accurately to measure and replace daily fluid losses, permitting time for the fistula to heal Too, fistulas are now more often closed surgically

Specifically, then, the important measures in the management of a small bowel fistula are the following (1) nothing by mouth (since it will merely escape through the fistula), (2) intravenous fluids to maintain adequate hydration, estimating daily volume requirements on the basis of measured losses as well as skin turgor and other clinical phenomena, (3) estimation of osmolar requirements on the basis of measurements of the plasma sodium chloride, and carbon dioxide combining power, (4) utilization of catheter suction with a small pump or wall suction to collect all possible drainage from the fistula, (5) correction of acidosis, should it develop, (6) nasogastric suction (this may or may not be employed) (7) protection of the skin

The mortality from duodenal fistulas is still high

Aspiration of the fistulous drainage results on the one hand in a better measurement of actual fluid losses and, on the other hand it tends to protect the skin of the patient from the irritating effects of the fluid from the fistula The skin surrounding the fistula can be further protected with aluminum paste, zinc oxide, or Amphojel dehydrated to a paste in a boiler over a hot plate If an adequate urinary output measurement cannot be otherwise achieved the use of an indwelling Foley catheter is justified. The basic therapy in intestinal fistula

is usually that of a holding action only, to gain time for the fistula to close However, if the fistula is not too high it may be possible to anastomose around the defect, excising the fistulous loop later Or, one may boldly attack the fistula itself, excising it and performing an end-to-end anastomosis, for there is an increasing awareness that one can often attack fistulas surgically with success Still again, a duodenal side fistula may be treated by gastric resection (Billroth II), converting the side fistula to a well drained end fistula, oral feeding is made available by the gastrojejunostomy As seen, a low fistula may be bypassed, if not excised outright, at an initial operation Here it is helpful to have introduced preoperatively a Miller-Abbott tube whose tip has been advanced to the point of the fistulous opening in the abdominal wall Under these circumstances, any loop that one finds containing Miller-Abbott tube is proximal bowel and any loop that does not contain Miller-Abbott tube is distal bowel This can prove a most helpful aid when dense and widespread adhesions render dissection difficult Following the bypassing procedure, it is surprising how little fluid continues to drain from the fistula, most of it going down the bowel in the usual fashion When the patient's nutrition has been improved and general health regained, a secondary operation may be employed to excise the fistulous loop One other technic which is at times successful is that of passing a nasogastric or Miller-Abbott tube to a point beyond the fistula, to permit feeding of the individual This is preferable to a "feeding jejunostomy," when it works

Biliary and Pancreatic Fistulas

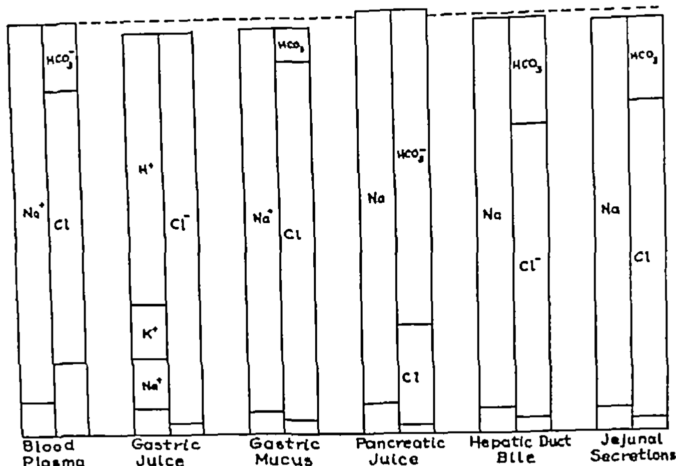
The volume of fluid lost from a pancreatic fistula or from a complete external biliary fistula usually ranges in the neighborhood of from 1000 to 2000 cc per 24-hour period However, water and salt depletion are more frequently associated with biliary fistulas than with pancreatic fistulas Two patients who had biliary fistulas developed marked sodium and chloride deficits, both of which responded promptly to adequate salt therapy, a third similar patient also had cirrhosis, and it proved extremely difficult to correct the low salt syndrome that developed in this individual

The external biliary fistula usually results from injury to the common bile duct, and may continue indefinitely if there exists obstruction below the point of injury or if the common bile duct has been completely severed However, eventually the proximal portion of the duct is likely to undergo cicatricial stricture formation, bile drainage ceases, and the patient becomes jaundiced Occasionally, excessive bile loss occurs through a T-tube even when no distal obstruction is demonstrated on cholangiography Under these circumstances the T-tube may be clamped or, if leakage then occurs around it, the tube may be removed—provided that the cholangiogram has revealed no obstruction

In contrast, the *pancreatic fistula,* while less depleting from a fluid balance standpoint, is a more vicious problem from the standpoint of total patient management Many pancreatic fistulas close spontaneously in a matter of days or weeks, but many others result in intra-abdominal sepsis, especially if in association with small bowel defects, and death finally ensues Pancreatic juice is an alkaline material and the volume ranges from 1 to 1 5 L per 24 hours (Fig 28)

Renal Insufficiency

ACUTE RENAL DECOMPENSATION Acute renal failure occurs on all surgical services from time to time, and there are two particular predisposing circumstances to which the clinician should be alert The first of these is the borderline renal function which may exist in a patient coming to elective major surgery, particularly in the elderly individual While renal function may be adequate for the patient's needs at his usual occupation and way of life, the further imposition of the insult of anesthesia and



Electrolyte Composition of Various Gastrointestinal Fluids (Gamble, J L *Chemical Anatomy Physiology and Pathology of Extracellular Fluid* 1947 courtesy of Harvard University Press.)

Fig 28 While the proportions of the several ions vary among the different types of fluids, the total ionic concentrations are remarkably similar Thus iso-osmolarity of the different body fluids is preserved

major surgery may result in renal insufficiency from which the patient may not recover Accordingly, it is our firm rule to request at least a nonprotein nitrogen (NPN) or a blood urea nitrogen (BUN) measurement prior to surgery in all patients above the age of 50 The reason for this is that if renal compensation is found to be borderline, the anesthesia or the extent of the operation may be altered or a purely elective procedure may be abandoned entirely All of us have seen patients with borderline renal function slide into chronic renal failure following operation, from which they never fully recovered. Such patients must often drink large volumes of water daily if they don't, the functioning nephrons remaining will not be able to clear the blood of the metabolites and a state of uremia will ensue If the NPN or the BUN is at the upper limits of normal in a patient above the age of 50, further studies should include at least a phenolsulfonphthalein (PSP) test and usually a urea clearance An elevated serum creatinine level is apt to have a more sinister connotation regarding renal reserve than a single elevated NPN, the latter being more readily affected by dehydration, bleeding into the bowel, adrenocortical insufficiency, and factors other than serious renal insufficiency Needless to say, the urinary specific gravity is not to be ignored

ACUTE RENAL SHUTDOWN The second type of renal failure that is likely to be encountered in the surgical patient is that of acute renal shutdown. In general, the patients in whom acute renal shutdown occurs are those who have suffered prolonged bouts

of hypotension, severe crushing injuries, severe infection, mismatched blood transfusion, or the ingestion of some toxic substance such as bichloride of mercury The renal lesion which results has been variously termed "necrotizing nephrosis," "crush syndrome," "lower nephron nephrosis," or "hemoglobinuric nephrosis" However, despite the variety of circumstances under which acute renal failure may occur, Lucke[30] studied a large number of cases during the second World War and pointed out the remarkable similarity in the renal lesion produced under different etiologic circumstances Oliver and his associates[44] later demonstrated that in acute renal failure two distinct types of tubular injury are encountered in varying proportions, depending upon the clinical insult The first type, *nephrotoxic necrosis,* is the predominant *lesion in renal failure following the injection* of a toxic substance excreted by the kidneys, such as bichloride of mercury Structural changes are limited to the proximal tubules and consist of varying degrees of damage to the epithelial cells without disruption of the basement membrane Both kidneys are equally affected and all nephrons are involved As one might expect, the pathologic picture is consistent with the filtration of a foreign toxic substance through the glomerulus and its absorption by the cells of the proximal convoluted tubules, where the intracellular concentration leads to death of the cells The basement membrane and the cells of the distal portion of the nephron, being functionless in regard to the toxic substance, are not affected

Oliver and his associates termed the second type of lesion *tubulorrhexis,* and considered it the predominant lesion in acute renal failure following crushing injuries or shock The damage occurs at random among the nephrons and in any part of the nephron, and is characterized by localized destruction of the entire tubular wall In this lesion the basement membrane is broken so that the lumen lies open to the intertubular connective tissue where an inflammatory reaction can occur The tubulorrhexic type of lesion was attributed to renal damage secondary to circulatory collapse In contrast, in nephrotoxic necrosis the integrity of the basement membrane permits an orderly regeneration of the tubular epithelium It appears that the number of nephrons affected in shock is directly related to the period of renal ischemia, and that the sooner the renal blood flow is increased the better is the chance for ultimate recovery

Even so, despite the fact that two types of lesions can be produced experimentally, the nephrotoxic and the tubulorrhexic, it is rare that either one or the other of these conditions will be found present alone clinically, since even in toxic poisoning the associated vascular spasm is enough to produce, in addition to the nephrotoxic necrosis *from the drug, a prolonged ischemia which* results in a certain degree of tubulorrhexis

It is of considerable interest that Mueller and Mason,[43] using the electron microscope have been able to demonstrate differences in the ultramicroscopic changes produced by different agents which produce lower nephron nephrosis That is, renal injury produced by one agent resulted in microscopic changes which were clearly different from those produced by another agent

Management of Acute Oliguria

CLINICAL MANIFESTATIONS The clinical course of acute renal shutdown may be summarized as follows The oliguria, proteinuria, hematuria and decreasing urinary specific gravity usually begin within hours of the causative event A period of severe oliguria of a few days to a few weeks duration is associated with increasing clinical and chemical evidence of renal failure In successful cases this is followed by a period of rapidly returning function and excretion of water, inorganic ions, and metabolites accumulated during the oliguric period The *oliguric phase* is followed by the *diuretic phase,* the period during which clinical improvement and the return o

renal function is rapid The "diuresis" consists largely of excess fluid that has accumulated from intake plus the combustion of body tissue

Swann and Merrill[*] have emphasized that the transition from the oliguric to the diuretic phase is of major importance in limiting the incidence of the morbidity and mortality from the complications of the oliguric phase The average duration of oliguria in acute renal failure is from 10 to 12 days, and during this phase the prominent symptoms and signs are those of cardiovascular, gastrointestinal, neuromuscular, and cerebral dysfunction *Cardiovascular* changes consist of the development of arterial hypertension, pulmonary edema and cardiac failure that results from hyperkalemia It is now accepted that the elevated plasma potassium concentration is a major threat to life during the oliguric phase *Gastrointestinal* symptoms consist particularly of anorexia, vomiting and diarrhea, often with distention and not infrequently with hemorrhage *Cerebral* and *neuromuscular* dysfunction result first in somnolence but later in stupor, delirium and coma Some patients manifest convulsions, though in our experience this has not been a major problem Neuromuscular findings may be those of weakness and hyporeflexia progressing to paralysis of the limbs and of respiration Areflexia and paresthesias of the extremities, lips and tongue—progressing to anesthesia—may develop Some fever and leukocytosis are common Anemia usually appears whether due to hemorrhage, increased red cell destruction or to depressed bone marrow function.

PRINCIPLES OF TREATMENT *Therapeutic objective* The problem is *to maintain life until the cells of the renal tubules have had time to regenerate*, for if regeneration does not occur the patient is doomed regardless of therapy To begin with it must be appreciated that the kidneys cannot be "forced" to excrete urine by the administration of large amounts of water during the oliguric phase and one can only try to maintain the patient in the best possible general condition while renal tubular (and glomerular[*]) repair is taking place With this fact firmly in mind, let us examine the means which over the past decade have proved useful in achieving these requirements

Fluid intake There can no longer be the slightest doubt that excessive fluid administration has in the past been a major cause of early death in these patients Stock[31] has estimated that by careful conservative management without dialysis, and in particular by the limitation of fluid, one can yield a recovery rate of approximately 80 per cent While we do not agree with this high figure, we would certainly agree that limitation of fluid is important Specifically, then, the fluid intake should usually be limited to not more than 800 cc per day, plus estimated losses by whatever urine is excreted vomitus, and stools If excessive sweating does not occur (at times it does), the daily intake of 800 cc plus measured losses is a practicable volume Actually, it has recently been our practice to weigh these patients on litter scales each day and to allow the loss of 1 lb of weight each day The reason for allowing weight loss is that, were the body weight to be maintained constant without variation the continued combustion of tissue with water formation would result in overhydration for the combustion of tissue liberates a considerable volume of water If litter scales are not available the patient can usually stand on ordinary hospital scales for the first few days of the illness, before disorientation and profound weakness occur Otherwise the rule of giving approximately 800 cc plus measured losses of fluid each day is helpful As noted if sweating is profuse and body weight cannot be followed the clinical evaluation must still remain an important guide in fluid administration (Fig 23)

Aside from the *volume* of fluid to be given, the *type* of fluid is important. Since the patient is not losing much salt unless he is vomiting the daily fluid requirements are given as glucose solution, ranging from 10

to 40 per cent, depending upon the size of the vein into which the polyethylene catheter has been introduced The patient will not often develop a serious sodium deficit during oliguria, unless this ion is needed for the neutralization of the organic and fixed acids derived from tissue breakdown

Acidosis is treated with oral or intravenous sodium bicarbonate

Caloric intake If the patient can eat he is given a diet containing much fat and carbohydrate, in a small volume of fluid Unfortunately, most of the patients that we have treated have eaten little after the first day or so, and usually the intravenous route has been used for both nutrition and hydration The objective of the nutritional intake is, of course, to diminish tissue catabolism by the protein sparing action of the calories introduced in the form of carbohydrate and fat The catabolism of 70 gm of tissue protein, as might occur in one day's total fast, releases approximately 140 mEq of nonexcretable potassium [13]

It has been found that the catabolism of tissue protein can be spared, in considerable measure, by the provision of at least 400 calories daily in the form of glucose or invert sugar Actually, it may be possible to provide intravenously or orally a diet of somewhat more than 400 calories, often approximately 1000 calories However, again, if the patient cannot tolerate oral feedings (and the most severely ill usually cannot), it will be very difficult to introduce many calories by intravenous feeding, since the volume of fluid required would endanger the objective of avoiding overhydration The introduction of a polyethylene tube into a femoral vein or into the superior vena cava is well tolerated, and through this polyethylene tube lying in a large vein one can introduce 30 to 40 per cent glucose solutions without causing serious thrombosis Recently, plastic tubing has become available which may be left in the vein for many days without causing difficulty If inflammatory phlebitis does develop, this can constitute a genuine threat in these patients whose antimicrobial capacities are depressed In addition to the hazards of septicemia, the fever caused by infection will increase tissue breakdown liberate additional potassium But for emphasis, the use of plastic tubing wil crease the conservation of veins, and is a matter of practical importance in t patients who, if they live, will freque require intravenous maintenance for at l two weeks and possibly longer

Potassium intoxication Hyperkale with its deleterious effect upon myocar function, is now recognized as a major ca of death in acute anuria, particularly in tients who are not overhydrated The ports of Merrill,[38] of Teschan and his ass ates,[54] and of Meroney and Herndon[36] pertinent Of these, the report of Mero and Herndon is particularly helpful in lining the management of potassium int cation Normally, the potassium libera by the catabolism of tissue cells du fasting is readily excreted by the kidn However, this cannot occur during peri of anuria and, furthermore, the coincide of massive trauma and serious infectio a particularly effective way of causing ra elevation of the plasma potassium level the oliguric individual Compromised tiss whether permanently destroyed or tem rarily embarrassed by trauma, infecti chemical or physical agents, or hypoxia, leases potassium to the plasma [10]

Under the previous discussion of pot sium metabolism, the statement was ma that we relied upon the plasma potassi level as determined by flame photometry more than upon the ECG, in judging t presence or absence of potassium deficien Nevertheless, it has been repeatedly point out that in potassium intoxication (rep senting potassium excess) the effect up the heart may be apparent from the EC before the plasma potassium level has ris significantly above the upper limit of no mal Moreover, improvement in the cardi function, as reflected in the ECG, may achieved in the absence of a significa lowering of the plasma potassium level reason for this is that the ECG reflects t net effect of various ionic influences up

myocardial electrical activity, the toxic effect of potassium is potentiated by a lowered plasma calcium and/or sodium level In other words, if there is a calcium deficiency with hypocalcemia, the toxic effects of an elevated potassium level, as indicated by the ECG, may be out of proportion to the degree of elevation of the plasma potassium level Meroney and Herndon called particular attention to the fact that the retention of inorganic phosphate in anuria results in a fall in the plasma calcium level Accordingly, the replacement of a calcium deficit may produce a striking improvement in the ECG which then reverts to that degree of abnormality characteristic of the plasma potassium level present at the time It was cautioned that calcium and digitalis appear to have an additive effect in their antagonism to potassium (in influencing the myocardium) and that care should be exercised not to give digitalis and calcium simultaneously Ordinarily calcium strengthens myocardial tone and contractions and potassium has the opposite effect In the presence of potassium intoxication the infusion of calcium in the form of calcium gluconate may cause prompt improvement in the electrocardiographic evidence of potassium intoxication and in the over all clinical picture

In general, progressive potassium intoxication may cause no symptoms until it has reached the stage at which the ECG shows severe deterioration and in the Korean experience patients who had symptoms with a less abnormal ECG were found to have other causes for their symptomatology [36]

The plasma *sodium level* also influences the electrocardiographic evidence of potassium intoxication It has been noted previously that there exists a physiologic antagonism between sodium and potassium and that raising the sodium level may result in a fall in the plasma potassium concentration. A sodium infusion may modify the electrocardiographic effects of potassium intoxication even when the plasma potassium level does not diminish In potassium intoxication, Meroney and Herndon found it possible to produce an almost normal ECG by the infusion of sodium chloride—even though the plasma potassium concentration was still 7.2 mEq /l Similar results were obtained by the infusion of calcium

Other measures by which the plasma potassium level can be altered The administration of *hypertonic glucose solution,* with or without insulin, results in the movement of potassium and phosphate into the cells, as both are incorporated into the glycogen carbohydrate complex If this procedure is to be employed to ameliorate the condition of potassium intoxication, it is recommended that the infusion be given continuously rather than in intermittent doses

Oral ion exchange resins should theoretically be useful, given by mouth in removing potassium from the body but, practically speaking they have often not been particularly helpful, since many patients with severe renal insufficiency are unable to retain these agents They may also be given by enema

Antibiotics It is judicious to give antibiotics prophylactically to these patients to diminish the likelihood of concurrent infection, particularly pneumonia, which would impose further metabolic strain upon the anuric individual

USE OF THE ARTIFICIAL KIDNEY The experience of the Renal Insufficiency Center in Korea did not indicate that the kidney" was usually necessary for the treatment of hyperkalemia alone, and whether to use the artificial kidney was determined largely by the clinical course of the patient After a period of oliguria usually from five to eight days the *syndrome of clinical uremia* began to develop The patient gradually became lethargic and showed evidence of mental torpor with tremulous and hyperreflexic extremities The nausea that had been present frequently progressed to active vomiting and retching and intractable hiccups were common Clinical manifestations of uremia first appeared in the patients of Meroney and Herndon when the blood NPN level

was approximately 250 mg per 100 cc In general, this level was reached approximately one day after a level of 200 mg had been exhibited, allowing plans for dialysis It was the practice to utilize dialysis when the NPN level reached 250 mg. per 100 cc, six hours of dialysis producing dramatic relief of symptoms as well as restoration of electrolyte balance Dialysis was then repeated as soon as the previous degree of uremic symptomatology had again been reached In Korea, dialysis was performed one or more times in 27 of 46 patients treated for acute renal shutdown—14 had dialysis once, 6 twice, and 7 three times

It was the common experience that renal insufficiency resulted in an NPN level which rose gradually to the critical level of 250 mg per 100 cc over a period of approximately one week In general, when relatively severe symptoms had appeared dialysis was performed In a few patients dialysis was delayed, and after a day or so more threatening clinical manifestations such as coma, convulsions, and pericarditis appeared In some patients dialysis was avoided because diuresis occurred before clinical uremia had appeared, and in others the use of measures to control hyperpotassemia made fewer dialyses necessary In the presence of clinical uremia no attempt was made to control potassium further by medical means, because dialysis was otherwise indicated and was effective in removing potassium The principal advantage of the medical control of hyperpotassemia (hyperkalemia) was to allow time for removal of the anuric patient to the Renal Center, or to permit more orderly management of the clinical uremia itself

Anemia and hemorrhage Recent studies have shed little further light upon the bleeding tendency which has long been recognized clinically in uremia The group in Korea found no abnormality in the clotting mechanism, only increased capillary fragility Unlike other manifestations of uremia, artificial dialysis had little effect upon the bleeding tendency, and it was frequently worse after spontaneous diuresis had begun The administration of vitamins C and K or fresh blood transfusions appeared to have little effect upon the diathesis Despite the fact that increased potassium levels might result from transfusion, small transfusions were given to the extent of 200 to 300 cc. daily to correct anemia and had little apparent deleterious effect (There is, incidentally, recent work indicating that the increased plasma potassium concentration which develops in stored blood may be reduced by the proper use of resins) The bleeding tendency caused concern when dialysis needed to be done, but it was eventually found that this need constitute no contraindication to necessary dialysis for uremia

Prophylactic management of hyperkalemia in traumatic injuries It was further appreciated during the Korean experience that it is utterly mandatory to effect adequate debridement of devitalized tissue as a therapeutic measure to prevent hyperkalemia and infection which would further diminish the chances for recovery of the patient in acute renal failure It was noted that while aggressive debridement might result in the sacrifice of some viable tissue, the failure to perform an adequate debridement might well prove fatal It was further again confirmed that it was impossible to control infection in devitalized tissue with antibiotics, since the blood supply of such tissue would not bring the antibiotics to the site of bacterial growth In all surgery, adequate debridement and drainage are essential if infection is to be controlled, regardless of antibiotic therapy

Stage of diuresis If the patient survives the period of oliguria and regeneration of the renal nephrons occurs, diuresis will begin This is usually heralded by an increase in the urinary output to greater than 1 L per day, following which it may steadily climb to several liters The volume of fluid diuresed depends to considerable extent on the volume of water that has accumulated during the period of anuria During diuresis the kidneys have apparently little capacity to conserve sodium chloride, and a sodium deficiency or "low sodium syndrome" may

lop For this reason, it is of importance llow the plasma electrolytes and to sup-odium chloride and, where needed, po um to these patients during this re-ry period The fortunate clinical fact at at this time appetite is rapidly re-ed, and once the patient is on a sub tial diet the problems of salt and other itional maintenance rapidly resolve nselves

rognosis of acute renal shutdown with of artificial kidney While the advent of blood dialysis has improved the out in many patients the mortality in te renal failure is still high The over all tality rate in 51 patients treated in the al Insufficiency Center in Korea was 53 cent However a serious complicating tor in these soldiers was the presence of ere wounds, often infected

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Chapter 3

Surgical Nutrition

In discussing nutritional problems in surgery, the following topics will be considered importance of nutrition in surgical patients, methods for studying nutritional processes, factors that influence spontaneous food intake, functions of dietary components in metabolism special nutritional problems in surgery, and routes and materials for therapeutic alimentation.

Importance of Nutrition in Surgical Patients

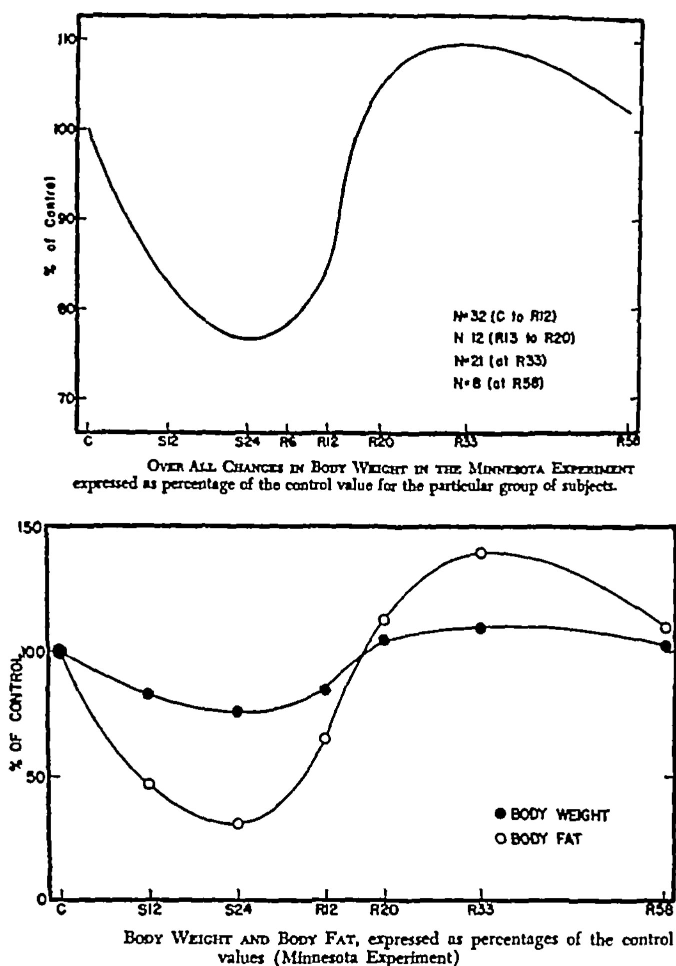
General Considerations

Virtually no system of the body is unaffected by nutritional deficits, though a given deficit may affect one organ more than another Caloric inadequacy results in the loss of body tissue and weakness of the muscular system The chief sources of calories in the diet are carbohydrate and fat. A deficiency of protein over a suitable period of time results in deterioration of the actual cellular structure of most organs of the body While the primary function of dietary fat is to supply calories fat is also essential for certain types of normal growth

Effects of Experimental Human Starvation

Physicians present at the time have studied the effects of mass starvation in various countries of the world. Yet, conditions were usually not conducive to careful physiologic measurements throughout the development of and recovery from, the starvation. Therefore, the careful experimental studies of Keys and his associates[14] were of particular significance and interest. These workers placed 36 human volunteers on a fixed diet which was below daily minimal requirements and then followed various physical and physiologic indices during the ensuing weeks, later the subjects were refed. Prolonged undernutrition which produced a body weight loss of more than 50 per cent resulted in emaciation, weakness, apathy, reduced metabolism, bradycardia and a tendency to develop edema. For the first three months of the control period these individuals required slightly more than an average daily intake of 3150 calories to maintain balance The mean daily intake of protein was 110 gm. and fats supplied about 30 per cent of the calories A semistarvation diet of approximately 1800 calories was then begun and was based on the food items used in Europe in times of famine such as potatoes, turnips, and coarse cereals, with only minute amounts of meats and dairy products

WEIGHT LOSS In Figure 29 are shown the average body weights in semistarvation and in the first 12 weeks of rehabilitation of a group There was a mean weight loss of 16 8 kg. (37 lb), which represented 24 per cent of the control body weight The actual loss of body tissue however, was considerably more than this, being somewhat obscured by the development of edema and a general state of excess water in the body At the end of the semistarvation period there was an average of about 12 to 16 lb of excess water in the body, so that the real tissue loss was close to 50 lb per man



OVER ALL CHANGES IN BODY WEIGHT IN THE MINNESOTA EXPERIMENT expressed as percentage of the control value for the particular group of subjects.

BODY WEIGHT AND BODY FAT, expressed as percentages of the control values (Minnesota Experiment)

Fig 29 Body weight curves during controlled starvation and realimentation ($S24$ = 24 weeks of starvation and $R12$ = 12 weeks of re-alimentation) Note that fat loss was a prominent feature during starvation and fat gain conspicuous during re-alimentation (see text) (From KEYS, A, BROZEK, J, HENSCHEL, A, MICHELSON, O, AND TAYLOR, H L *The Biology of Human Starvation,* Vol I Minneapolis, The University of Minnesota Press, 1950)

BLOOD VOLUME The total blood volume was not markedly altered, and there was an actual increase in plasma volume It is known, of course, that the malnourished individual may have an almost normal blood volume, due to the fact that the plasma volume may be normal or increased Nevertheless, a severe anemia may at times be present, and this is the important point in view of the fact that there must be adequate hemoglobin in adequate numbers of red cells to carry oxygen to the tissues

MUSCULAR STRENGTH Much of the weight loss in Keys' patients was from the muscles, and there was marked weakness, particularly seen in tasks requiring any endurance The loss in strength for a single muscular contraction amounted to only about 30 per cent, but the loss in capacity to continue work which would not ordinarily result in exhaustion in a few minutes was close to 80 per cent The speed of small muscular movements, however, was little affected, and the loss in neuromuscular coordination was considerably less than that in strength

CIRCULATORY CHANGES The shrunken heart (evaluated by roentgen examinations) beat slowly but regularly, and there was evidence that circulatory function was better preserved than muscular function There was some decrease in blood pressure (a common finding in patients who come to the hospital in a starved condition), and there was a remarkable resting bradycardia, the average heart rate in basal rest being 35 beats per minute after 12 weeks of semistarvation and 37 at the end of 6 months It was noted that this slow heart rate differed from the bradycardia of beriberi in that exercise did not provoke an excessively fast heart rate in the starved man Moreover, the small heart of starvation contrasted sharply with the big heart of beriberi

The efficiency of circulatory reflexes, especially as regards readjustments to changes in posture, was impaired by the prolonged period of semistarvation

PSYCHIATRIC CHANGES The mood of most of the experimental subjects gradually changed to one of mild depression, a preoccupation with food, and loss of sexual interest

SOME MISCELLANEOUS OTHER EFFECTS OF STARVATION *Hepatic function* and structure are often altered in starved individuals, and certain types of protein deficiency may result in cirrhosis Many starved persons exhibit deranged absorptive patterns for foods placed in the *intestinal tract,* and some have an actual intolerance for certain items of diet The mucosal pattern of the small intestine may be abnormal on roentgen study The activity of various *endocrine organs* is diminished in starvation Perloff and his associates[21] have emphasized the rôle of starvation in producing hypopituitarism, and starvation is an important etiologic factor

in the syndromes referred to as Simmonds' disease and anorexia nervosa, in fact, the functional hypopituitarism produced by starvation may be difficult to delineate from hypopituitary cachexia due to structural impairment of the anterior pituitary gland in Simmonds' disease The other endocrine organs whose activity is regulated by the pituitary will have altered function in the presence of depressed pituitary function It has been shown that a low calorie diet for one week may lower the basal metabolic rate as much as 10 per cent In starved individuals the daily urinary excretion of adrenal corticoid substances is low normal, but the excretion of 17 ketosteroids is usually markedly diminished reflecting at least a qualitative alteration in adrenocortical activity It has also been stated that a diet deficient in vitamin C results in a diminished insulin content of the pancreas[5]

Nutritional anemias may be encountered Deficiencies of iron folic acid, or vitamin B_1 may cause anemia but protein deficiency may also do this The intimate relationship which exists between the formation of hemoglobin plasma protein, and cell protein was delineated by the classic studies of Whipple and Madden.[32]

Hogan[10] has called attention to evidence that maternal malnutrition may possibly result in an increased incidence of congenital malformations, and that there may be a relation between maternal nutrition and the functional activity of the brain of the progeny certainly it would appear that the functional activity of the central nervous system in rats can be impaired by some type of inadequacy in the maternal diet. The question was also posed as to whether there is a correlation between economic level and intelligence it was suggested that the cause and effect are reversed in public opinion and that some of the stupid are stupid because they are poor

The foregoing thoughts are offered merely to indicate the extremely broad scope of nutritional influences in the surgeon's patients The well nourished patient who comes to operation in a good frame of mind, with a determination to come through safely, will usually represent a better surgical risk than the starved individual who comes to operation mentally depressed and with little physiologic reserve

Malnutrition may occur even when the oral intake would be adequate for normal activity in the healthy individual Such a circumstance would exist when bowel absorption is poor, as in pancreatic insufficiency, total gastrectomy, or following extensive small bowel resection, in circumstances where nutritional needs are much increased as in prolonged fevers or hyperthyroidism where abnormal losses occur, as in open wounds small bowel fistula, burns or purulent conditions and where metabolic use of foodstuffs is inefficient, as in diabetes mellitus

Special Surgical Problems Resulting from Nutritional Inadequacy

POOR TOLERANCE FOR OPERATIVE STRESS AND DELAY IN CONVALESCENCE. Patients with nutritional deficiencies require a longer time for convalescence than those whose nutrition has been maintained There is abundant evidence in the literature to indicate that the disability which follows surgery, traumatic injury, or disease is significantly prolonged by malnutrition

POOR WOUND HEALING The state of nutrition plays a rôle in the healing of wounds, and it has been demonstrated that proteins, vitamin C, riboflavin, and vitamin A are all important in this respect. Moreover, the patient with protein deficiency is prone to postoperative wound disruption. *Skin grafts* which take poorly in the malnourished and anemic individual may be successful when the nutritional status has been improved. The incidence of *decubitus ulcers* (bed sores, pressure sores) has been correlated with a protein deficit in many instances, but good general nursing care is also a major factor in reducing the incidence of bed sores

INCREASED SUSCEPTIBILITY TO INFECTION AND LOWERED RESISTANCE TO DISEASE. Semi

starved and starved individuals are highly susceptible to the development of infections of various types (Chapter 5) In part, this is due to a diminished ability of the host to form antibodies, for when depleted animals are passively immunized they tend to survive infections as well as normally nourished controls In addition to low antibody titers, actual changes in the tissues of starving individuals may explain their increased susceptibility to infection Superficial necrosis of the mucous membrane of the respiratory tract, the gastrointestinal tract, and the skin frequently is seen, and this break in continuity of normally protective surfaces makes a ready portal for the organisms which are always present The combination of a weakened tissue barrier, a decreased capacity of the malnourished bone marrow to form leukocytes of both the granulocytic and the lymphatic series, and a decreased immunologic response to invading organisms accounts for the increased severity of infection (increased "virulence") in the malnourished individual[22] Among the many infections which progress more rapidly in the presence of poor nutrition, none is better documented than that of pulmonary tuberculosis (p 127)

Disturbed Organ Function—Further Comment

It has been seen above that the gastrointestinal tract is frequently affected by malnutrition Anorexia may develop early in the course of generalized vitamin or protein deficiency and leads to a vicious cycle This is seen in patients with thiamine deficiency, anorexia may appear in the patient with thyrotoxicosis who has an increased need for this vitamin due to the increased rate of metabolism We have found that forced tube feeding in anorexic burn patients may improve the appetite after a brief period of time

Disturbed gastrointestinal motility with the diarrhea that may accompany severe prolonged dietary inadequacy may become one of the most serious and difficult complications of malnutrition—and of re-alimentation This was an outstanding feature of attempts to feed liberated displaced persons in Germany at the close of World War II.

Nervous system lesions appear after various types and degrees of nutritional deficiency, as mentioned The sensorium may change and the individuals may become hypochondriacal and difficult to work with Furthermore, not only is the mental outlook considerably altered in malnourished states but definite organic lesions can be demonstrated in the peripheral nerves, such as the polyneuritis associated with thiamine deficiency

The *liver* contains less protein and often more fat in starvation, due to the mobilization of fat from the depots, this diminishes liver tolerance for certain forms of anesthetic agents It has been shown that young rats consuming low protein diets may develop necrotic livers, whereas adult animals develop fatty infiltration followed by incipient fibrosis[29] Under certain circumstances such liver changes may be reversed by the feeding of a more adequate diet, but if the adequate diet is delayed too long the lesions may become irreversible

On the basis of various studies, it would appear that in man the most important protective factors for the liver in an adequate diet are probably animal protein, choline, and methionine An adequate, balanced diet tends to protect the liver against injury and to promote regeneration of liver cells Such a diet should therefore be prescribed under circumstances in which liver injury is suspected or may be anticipated Yet, an adequate diet is only one of many factors which assist in preventing or managing liver damage

Enzymic activity may be reduced by caloric, vitamin, and protein deficits All enzymes and many hormones are either proteins or are combined with a protein molecule Furthermore, the vitamins, especially those of the B complex, are concerned with enzyme activity For example, protein deficiency may result in a decreased peptic

activity of the gastric juice, in a diminished renal phosphatase and succinic dehydrogenase, in a reduced xanthine oxidase activity in the liver, and in a reduced total concentration of hyaluronidase in the testes. Protein repletion re-establishes enzyme activity at a normal level.[23]

Hypoproteinemia eventually occurs when there is a prolonged negative nitrogen balance In the early stages of protein deficiency there is a reserve of protein available for mobilization, and this is used in an attempt to maintain normal serum protein concentrations Eventually, however the continued depletion of the body protein reserves will usually be reflected in a lowered serum protein level, particularly as regards albumin The return of the serum protein concentration to normal will thereafter be slow even with a good dietary intake since it is estimated that about 30 gm of protein must be deposited in the tissues before 1 gm is restored in the circulation Chronic hypoproteinemia results in an increase in the susceptibility to shock from hemorrhage due not only to qualitative and quantitative alterations in blood constituents but to the hormonal, cardiovascular and other factors that have been described

Nutritional Edema, Vitamin Deficiencies, and Specific Amino Acid Deficiencies

A severe protein deficiency is commonly associated with the development of edema This edema may be in a latent form which is not apparent unless the patient is weighed or it may be readily detectable on physical examination Yet, while a lowered serum protein is frequently associated with edema, extremely low serum protein levels may be observed in patients who have no demonstrable edema

It has been seen that the vitamins, accessory food substances are important in various physiologic activities, including reactions which involve enzymes The common clinical manifestations of specific vitamin deficiencies are known to all, including scurvy (C), beriberi (B_1), rickets (D), and cheilosis (riboflavin) Moreover, the vitamins are often closely interrelated, and a deficiency of one member of the B complex may affect the metabolism of other members of this complex As an example, hyperkeratotic skin lesions are said to be produced by a deficiency of Vitamin A, Vitamin C, niacin, or pyridoxine Glossitis and fissures of the tongue may be produced by deficiencies of one or more vitamins While cheilosis usually responds to riboflavin therapy, in some cases it heals only when pyridoxine is administered

Clinically, however, isolated or pure single vitamin deficiencies are rarely encountered, and if one vitamin deficiency is manifest it is to be expected that other vitamin deficiencies are also present. A possible exception is that of vitamin K deficiency, leading to a lowered prothrombin level Therefore, in the usual vitamin therapy a multivitamin preparation providing liberal amounts of all known vitamins is desirable

For the *construction of protein* it is necessary not only that a sufficient quantity of amino acids be present but also that the amino acids be present in the proper proportions A diet inadequate in a single "essential" amino acid may cause a specific deficiency syndrome as well as provoke a negative nitrogen balance In the adult human being tryptophane deficiency results in a loss of weight in an infant, ten days of tryptophane deficiency results in anorexia and a marked drop in plasma protein levels Two weeks of tryptophane deficiency in chicks have been shown to produce changes in enzyme activity which are reversible if an adequate quantity of the amino acid is subsequently provided[12, 24] Various other amino acids have likewise been shown to be specifically important. The significant fact is that whereas the body can itself form or compensate for the lack of some substances certain other nutritional requirements are highly specific and must be included in the diet.

Deleterious Effects of Overnutrition

Much has been stated regarding the undesirable effects of undernutrition or malnutrition, but overnutrition is likewise undesirable Generalized *atherosclerosis* with associated coronary artery disease, *diabetes mellitus,* and *hypertension* are far more common in obese individuals The presence of large amounts of fat often makes surgical exposure troublesome, and, particularly in operating for malignancy, it may be difficult to excise the desired tissues as accurately and as satisfactorily as in a lean individual The obesity is not limited to the body wall, of course, since it involves the mesentery of the bowel, the omentum, and the retroperitoneal area (Fig 73)

Fat contains little water and has a scant blood supply This results in a poor defense against infection, an all too common complication in the wounds of obese patients Po operative respiratory complications are al prone to develop in obese persons becau *of the fact that the diaphragm is forced u* ward by abdominal fat and viscera

Obesity Syndrome In Figure 30 a shown the major features of a syndron which may develop in extremely obese sul jects Thus, not only does the obesity pr dispose to the development of other di eases, it here constitutes itself a disea which can produce fatal cardiopulmonar complications

The Causes of Obesity

EXCESSIVE CALORIC INTAKE Obesity is us ally the result of a dietary intake in exce of energy requirements Simply put, t daily caloric intake of the sedentary ind vidual may be increased from 3000 to 50C

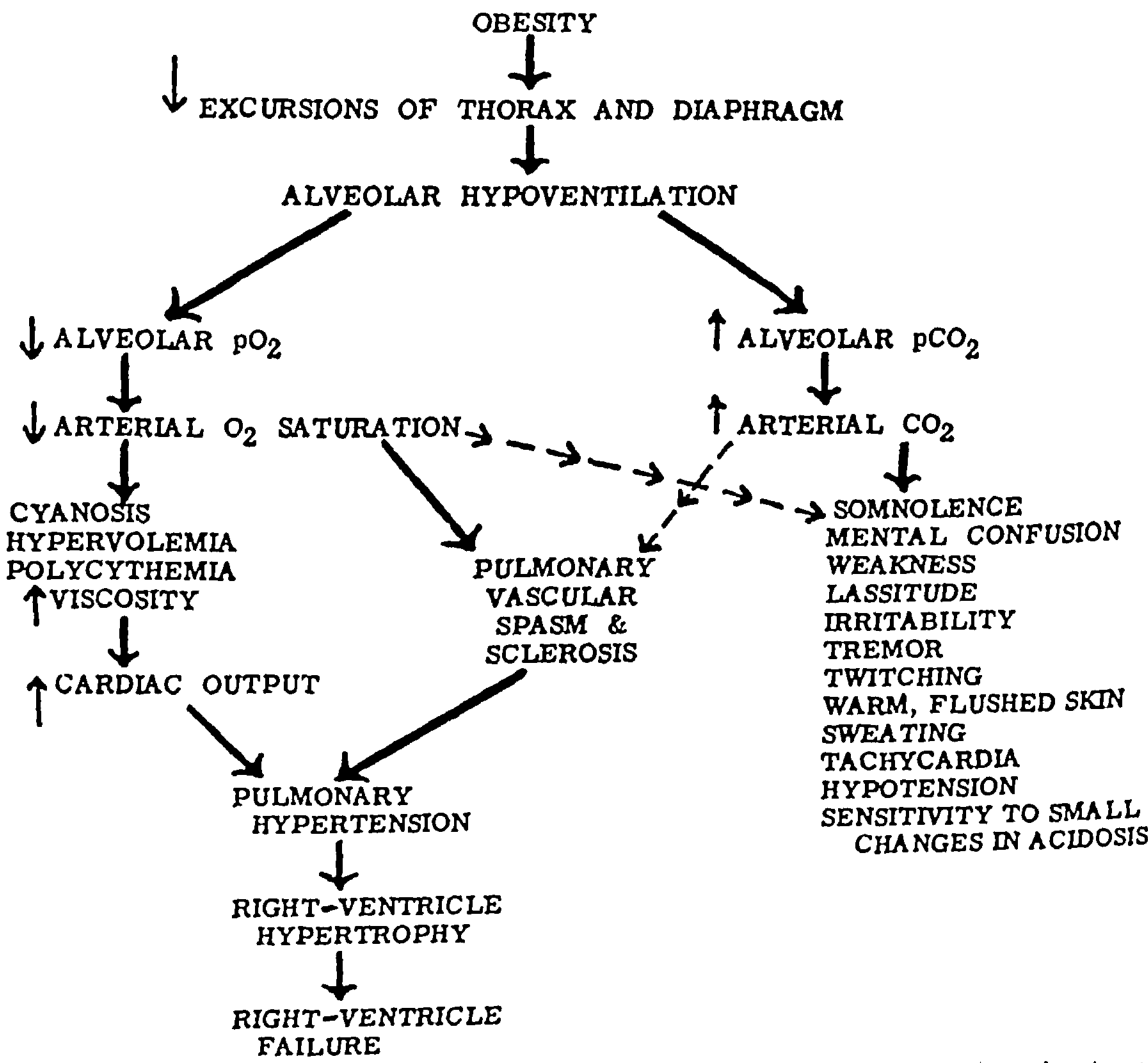


Fig 30 The obesity ("Pickwickian") syndrome (From SEIDE, M J Heart failure due to extreme obesity report of a case with autopsy findings New England J Med, 257· 1227, 1957)

without a body weight increase—provided that the man begins hard physical labor or exercises vigorously for several hours each day Otherwise, the accumulation of fat is reflected in an increase in body weight

It is frequently stated that obesity represents a component of a neurosis and this is certainly true of those compulsive individuals who must be nibbling when not otherwise occupied, including those persons whose unfulfilled emotional needs are assuaged by eating. Yet, the moderate obesity that is so common—the middle-age spread'—is largely the consequence of a persistence of the eating habits of the young adult into years when physical activity is declining. Moreover the metabolic rate and growth requirements decline with the advance toward middle age, and during this period hormonal changes other than thyroidal may also contribute to the development of obesity

OTHER FACTORS IN OBESITY The problem of obesity is being subjected to an increasing amount of experimental study, and some interesting facts emerge One type of obesity may follow overtreatment with adrenocortical steroids (Cushing's syndrome) Obesity can also be produced by certain lesions in the hypothalamus Furthermore, obesity runs in families, and genetically obese strains of mice have been developed Non obese littermates of genetically obese mice choose a low fat high carbohydrate diet while the obese mice choose a diet low in carbohydrate and high in fat An outstanding characteristic of the genetically obese mouse is its low level of activity However if forced to exercise the mouse does lose weight.[19]

Methods for Studying Nutritional Processes

CALORIMETRY AND RESPIRATORY QUOTIENT Nutritional processes may be studied in a variety of ways. For example, one can put the person inside a calorimeter and actually measure the amount of energy derived (as heat) from the metabolic usage of various types of foodstuffs This is a difficult and tedious process Recently the nutritional metabolism in surgical patients has been studied by means of a bedside collection of expired carbon dioxide over a timed interval, since the proportionate combustion of the three major foodstuffs (fat, protein and carbohydrate) is reflected in the CO_2 content of the expired air Kinney and his associates[17] found that a rate of infusion of at least 40 cal per hr was required to alter metabolism sufficiently to be detected by this method Of course, the more fat burned, the lower the respiratory quotient (R Q = O_2 used/CO excreted)

THE BALANCE STUDY The most widely used means of investigating body usage of individual foodstuffs salts, and water is the balance study In brief, the amount of the material ingested or infused is carefully measured as is its excretion in the urine and feces If during the actual study period more of the substance (nitrogen, for example) is ingested than is excreted, the individual is said to be in positive nitrogen balance if intake equals excretion he is in nitrogen equilibrium, if losses exceed intake he is in negative balance

While much fundamental information has been gathered by balance studies, this type of approach affords relatively little information regarding what metabolic pathways the substance took while it was in the body Modern physiologists are no longer satisfied merely to know how much of a substance was fed and how much of the substance was excreted they desire to know what chemical steps occurred in the protein molecule during the absorption utilization, and eventual excretion of its nitrogen Moreover, how long did an individual nitrogen atom remain in the body, on the average? Such information is not to be gained from the nitrogen balance study

ISOTOPIC TECHNICS Using radioactive and stable isotopes as tracer elements however, one can often identify the steps of degradation and excretion—or resynthesis and utilization—of the compound under study

For example, an amino acid can be synthesized which contains a radioactive carbon atom This amino acid is then fed to an animal and its progress through different chemical steps ascertained by suitable analyses of the excreta, blood, and organs of the animal The isotope technic has permitted the settling of numerous questions where the balance study would have failed

Isotopic studies have shown that the living cell is able to incorporate into itself, at a surprisingly rapid rate, the elementary chemical compounds out of which its protoplasm is constituted By feeding radioactive glycine, Rittenberg and his associates[23] were able to demonstrate that many labeled amino acids turned up in the various proteins of the body of the animal This was, of course, direct evidence not only for the interconversion of at least the amino group of the amino acids but also for the synthesis of new proteins

When a small amount of a labeled amino acid is added to the normal diet of an animal (or man) for a short period and the isotope concentration in the proteins investigated, it may be demonstrated that the isotope concentration in the serum proteins is increased This increasing isotope concentration mirrors a process in which labeled amino acids, either the one fed or others metabolically formed from it, are being incorporated into the serum proteins In a human experiment, Rittenberg and his associates[23] found that even though radioactive glycine (or the carbon tracer derived therefrom) appeared in the serum and other proteins, nitrogen equilibrium existed, indicating that degradation and synthesis proceeded simultaneously They found also that after cessation of the administration of labeled amino acids to their subject the isotope concentration of the serum proteins promptly began to decline It was further proved that glycine is utilized for the synthesis of the protoporphyrin of hemoglobin When labeled glycine was administered to a mammal, the hemin took up N^{15} This occurred, according to Rittenberg, because glycine is the specific precursor of hemin By suitable mathematic treatment it was possible to calculate the rate of destruction of the red cells, as a function of the period elapsed since their production For example, during the initial period after the labeled glycine was fed, the glycine was employed in the marrow to form labeled heme, which then resulted in labeled red cells. As these cells were released to the circulation the average isotope concentration of the entire circulating mass of red cells increased After 20 days this process fell to a negligibly small value For the next 80 days the labeled red cells produced during the first part of the experiment were destroyed, resulting in a decline of the isotope concentration of the total circulating red cell mass

These examples of the isotopic method have been given in some detail to illustrate the uses to which isotope technic can be put, for it is certain that our knowledge of cellular and tissue metabolism will be greatly extended by further use of these important tools

ENERGY METABOLISM AT THE CELLULAR LEVEL This brief survey of methods with which one may study nutritional problems should include reference to studies at a cellular level Obviously, most aspects of nutrition must eventually come down to the cellular level, and important studies are in progress Since bacteria represent single cells, an analysis of the metabolism of these cells can reveal much concerning fundamental energy processes The classic works of Lipmann[18] represent a case in point Utilizing various bacterial organisms as the experiment required, he was able to demonstrate that many of the basic cellular chemical reactions have as their primary components a surprisingly few important chemical linkages That is, there is increasing evidence that the living organism tends to use a standard type of chemical energy, derived from the phosphate bond Lipmann points out that if the cell uses a standard energy, then this presupposes a certain uniformity of processing He further notes that

if one focuses his attention on primary chemical linkages, it is discovered that the linkages in different classes of compounds are quite similar, that as an endlessly repeating process in the building up of cell material one finds the elimination of water between groupings One of the most common reactants in these condensations through intermolecular dehydration is the carboxyl group Quite generally, ester and peptide links appear to be formed by way of carboxyl activation The energy input necessary to perform these linkages as they occur in fat protein, and elsewhere is very similar, around 3000 cal Thus, in the field of biosynthesis one has the rare example of progress leading to simplification

The studies of Gunsalus[8] are also pertinent here Again, bacterial organisms and their metabolism and need for various nutrients were used to study the various compounds Specifically Gunsalus used bacterial growth to study vitamin B_6 The need of a certain strain of bacteria for a single amino acid in the nutrient medium may be extremely specific Thus by comparing growth in a standard synthetic medium containing a known amount of the specific amino acid with that in a medium (e g, urine) containing an unknown amount of the specific amino acid, one can analyze quantitatively for the amount of the specific amino acid contained in the unknown medium.

From analysis of such investigations there emerges a surprisingly consistent picture of the energy mechanism employed by cells for the synthesis of a variety of compounds ranging widely in their complexity The primary ways of forming the initial energy containing bonds by reactions coupled to oxidations appear to be relatively limited in number[27] Variety and flexibility in synthetic capacity are obtained by the evolvement of complex group transport mechanisms which by preserving the bond energy content make possible the reshuffling necessary for variety The basic building units especially in the formation of carbon skeletons, are very simple ones "In solving the problem of the fabrication of a complex molecule, such as a branched steroid, nature apparently prefers to weave from simple elements rather than stamp them out from more complex precursors"[27]

Summary

In concluding this section one may note that there is an enormous range in the types of studies that may be done in evaluating nutritional problems, methods which vary from one so simple as that of determining whether or not a person gains or loses weight on a particular diet, to one which utilizes a pure culture of a particular bacterial organism to study the metabolism of a single amino acid.

Factors That Influence Spontaneous Food Intake

Appetite

Despite the importance of the appetite in patient care, the locus of the appetite remains tantalizingly elusive Various types of evidence may be cited (1) Miller and Kessen[40] studied the hunger reducing effects of food by gastric fistula *versus* food by mouth They found that animals which received milk by mouth, either immediately or after a delay, learned faster than those which received milk by way of a gastric fistula The albino male rats used were given enriched milk when they went to the correct side of a simple T maze and isotonic saline when they went to the incorrect side (2) Janowitz and Grossman[14] found that the average daily volume of food ingested by dogs was not significantly modified by feeding small portions of sucrose solution, cream casein hydrolysate, alcohol, or bitters 20 minutes before the regular feeding. They also found that bulk rather than caloric content was the factor which diminished further food intake since the same bulk of cream containing from 73 to 172 per cent of the average daily caloric intake caused approximately the same decrease in food in

take as did a sucrose solution containing only 22 to 26 per cent of the daily caloric intake (These studies notwithstanding, it is certain that appetite is, at least in part, a diffuse metabolic phenomenon and not a function located entirely in the gastrointestinal tract As seen below, the *hypothalamus* is known to have much to do with the intake of food, as well shown in certain pathologic states) (3) Marked variations in food intake have been described in various species of animals following injury to certain parts of the hypothalamus, including an increased food intake produced by lesions in the region of the ventromedial nucleus, the hyperphagia induced leads to obesity Anand and Brobeck[2] were able to localize in the hypothalamus of rats an area which was intimately associated with appetite Bilateral destruction of this area led to a complete cessation of eating, but a unilateral lesion had no such effect Bilateral lesions involving either the ventromedial nuclei, or the region between them and the lateral area (but not involving the lateral area), produced hyperphagia and obesity Bilateral lesions in the other areas of the hypothalamus did not produce a change in food intake, with the exception that injury to regions adjacent to the lateral area might induce diminished eating for a few days after operation If the animal was made obese by medial lesions, eating ceased when the lateral areas were destroyed bilaterally This lateral area has been called a "feeding center" It may be responsible for the central hunger reaction or the urge to eat, while the ventromedial nucleus or some structure in its neighborhood may be capable of exerting an inhibitory control over the "feeding center" through fibers which run laterally to the lateral hypothalamic area (4) Gastric hunger contractions are rhythmic tonic contractions of the stomach which often reach a tetanic peak They appear in the newborn at birth and recur after feedings as the stomach empties They persist after vagotomy, though diminished in intensity, and are augmented by stimuli from the central nervous system induced by insulin hypoglycemia After vagotomy and alcohol block of the splanchnic nerves in rats, the hunger drive is maintained but is diminished in strength Hunger contractions persist in starvation, but the sensations of hunger diminish after the first few days After total gastrectomy a patient may not feel hunger pangs such as he had normally experienced, but he often will have a lively desire for food and will experience an emptiness in the abdomen Thus, the absence of these contractions or the blocking of the neural impulses from them does not rob the person of the desire for food, and their presence does not insure that he will experience such a desire They cannot, therefore, be regarded as an obligatory stimulus for hunger drive (5) Anencephalic children may accept and swallow sweet solutions but reject sour and bitter ones The decerebrate pigeon becomes restless and walks about his cage when his crop is empty, but when it is filled he quiets down and remains immobile These and other studies indicate that the reflex centers concerned in the acquisition of food are subcortical in location[15] The location of appetite centers in the hypothalamus was cited above (6) "Modifications of the hunger drive are produced by various forms of reflex conditioning in which the cerebrum primarily participates For the purposes of distinction and analysis of factors involved one may now define appetite as resulting from modification of the behavior of the hypothalamic hunger drive by cerebral activity"[15] Training and table etiquette and the social amenities of life under the guidance of parents are largely responsible for softening this aspect of hunger in children "Psychiatrists have taught that the hypothalamic biochemical definition of food has been extended widely by the cerebrum They point out that the nursing of a child is a complete ritualistic ceremony The fondling petting, and singing of lullabies by the mother comes to be food as realistically as the milk which trickles into the child's throat The child's tension for food cannot

be relieved by breast milk alone The tension for emotional gratification will remain unsatisfied"[15]

From these different types of evidence regarding the physiology of appetite, it is apparent that systematic knowledge of the factors governing food (and water) intake is difficult to obtain because of interlacing psychogenic, pathologic, and physiologic factors

Thirst[1]

The origin of the sensation of thirst is also far from settled Yet, here again, much has been learned (1) The dog with a complete esophageal fistula derives much relief from his thirst by drinking even though the water is lost to the outside through the fistula. (2) The burro will, upon reaching water drink at once a volume of water almost precisely equal to his water deficit (3) The patient in shock often complains bitterly of thirst. (4) Subjects depleted of water experience marked thirst whereas those depleted of salt do not Holmes and Gregersen[11] produced thirst by the intravenous injection of hypertonic solution This suggested that the sensation may arise, at least in part from an increased osmolarity of body fluids, and other evidence has indicated that the hypertonic solution stimulates central osmoreceptors Finally, Anderson and McCann[3] stimulated the hypothalamic regions of goats directly with small amounts of hypertonic saline solution (and on other occasions with electrodes) and with movies recorded most convincingly the enormous volume of water which repeated hypothalamic stimulation can force the animal to drink. Habit too is an important stimulus for water intake

Functions of Dietary Components in Metabolism

Protein

The primary function of protein foods is to supply the amino acids needed for the growth repair, and general maintenance of the structural and catalytic machinery of living cells"[4] Therefore, inasmuch as calories are available in the form of carbohydrate and fat—and some calories are normally derived from protein as well—the primary function of ingested protein is to provide the building stones for the lean tissues of the body Most past studies of protein metabolism have been based upon the nitrogen balance, the factor of 6 25 being used, that is, by multiplying the grams of nitrogen excreted in the urine each day by 6.25, one arrives at a useful approximation of the amount of protein which was metabolized to provide that amount of nitrogen Similarly, of course, by dividing the actual weight of protein ingested by 6 25 one derives a useful approximation for the amount of nitrogen contained in the diet during the period of consideration—though in balance studies it is advisable actually to homogenize an aliquot of each day's diet and analyze chemically for nitrogen content. Also, an estimate of protein catabolism can be gained by measuring potassium excretion, since the ratio of nitrogen to potassium is approximately 10 1

Body protein equilibrium, as reflected in the nitrogen balance, can be maintained by a high protein level and a lowered level of caloric intake in the form of carbohydrate and fat Or, one can markedly lower the protein intake, and, if the caloric intake remains unchanged, the body will eventually achieve a new nitrogen balance Or, it may be possible to maintain a nitrogen balance at the original high level, following reduction of the protein intake, if the caloric intake in the form of fat and carbohydrate is sufficiently increased However, regardless of the caloric intake, the protein in the diet cannot be reduced below a critical level, otherwise negative nitrogen balance ensues —for a certain critical level of protein intake is required to maintain the structure of the body cells and, if less protein is supplied, the tissues of the body will be catabolized. The *minimal daily protein requirement* for an adult lying quietly in bed is

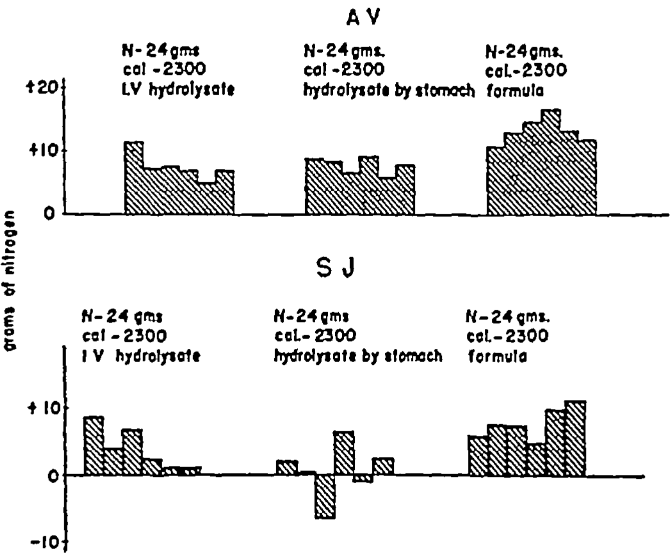


Fig. 31 Two questions are examined First, it is seen that the protein hydrolysate-glucose-alcohol solution was about as effective by vein as by mouth in both patients by vein more nitrogen was lost in the urine, and by mouth more nitrogen was lost in the stools Second, it is clearly apparent that the isocaloric, isonitrogenous whole food mixture was definitely more effective in achieving a positive nitrogen balance than was the protein hydrolysate mixture (From LOVELACE, J R, AND HARDY, J D Surgical nutrition I Intravenous *vs* oral route, nitrogen balance, a preliminary report Surgical Forum, **5**: 439, 1955)

from approximately 1 to 1.5 gm of protein per kg of body weight—at a caloric intake of from 25 to 30 cal per kg of body weight Even so, these figures represent basal requirements and must be revised sharply upward in the presence of fever, hyperthyroidism, unusual protein losses from wounds, after operation, and in other circumstances

RELATION OF AMINO ACID CONTENT TO FOOD VALUE OF PROTEIN The food value of a particular protein depends upon its amino acid composition The amino acids of most animal proteins are in proper balance for optimal nutritional effect in human beings, whereas plant proteins frequently provide a spectrum of amino acid composition and concentration which may not be optimal for human nutrition The fate and usefulness of various amino acids in the body have been examined by means of balance studies and by amino acids labeled with N^{15} or C^{14} Schoenheimer,[27] using N^{15}-labeled amino acids, showed that the rate of protein breakdown and subsequent resynthesis *in vivo* was far more rapid than had been supposed by previous workers Geiger,[8] among others, showed that the process of protein synthesis requires that the amino acids necessary to form the protein molecule be present simultaneously There is no mechanism thus far known whereby amino acids may be stored either individually or in polypeptide aggregates, as certain vitamins, fat, and carbohydrate (glycogen) can be stored Incomplete but supplementary mixtures of amino acids or proteins may fail to give nitrogen retention when separated from one another by a few hours, but do so when fed simultaneously

AMINO ACIDS VERSUS WHOLE PROTEINS IN HUMAN NUTRITION Satisfactory protein nutrition and nitrogen balance are achieved more readily by feeding whole proteins than by feeding amino acid mixtures of equivalent nitrogen content (Fig 31)

Fats

Fats have at least two main functions first, that of fuel reserves which are variable in amounts and, second, as an integral and constant part of the structure of living tissues For a long while it was considered that the fat of the body was relatively inert and that changes in its composition were very slow Yet, farmers had known for many years that the type of fat an animal deposited could be influenced by the diet he was fed In 1939, Schoenheimer and Rittenberg,[26] using isotopic methods, demonstrated conclusively that there was a constant turnover of fatty acids in the body, a process far more rapid than previously believed Since that time many studies of this type have confirmed the knowledge that the apparent constancy of the quantity of fat in the normal adult mammal results not from a chemical inertia of the fat depots but rather from the nice balance which exists between the processes leading to the deposition of fat and the processes leading to its mobilization, utilization, and excretion In

this connection, while the fatty acid composition of the fat deposited by farm animals can be altered by selective feeding, if permitted a wide dietary choice the animals will select those foods which form fat characteristic of the species

The forces which mobilize fat from the depots and cause it to be transported to the liver, and the factors which increase the rate of turnover of fat in the liver with resulting storage in the depots, are incompletely understood The fatty condition of the liver seen in starvation stress may be due in part to the action of a factor derived from the anterior pituitary and endowed with the specific capacity of accelerating the mobilization of depot fat[6] (Fig 73) The term *adipokinin* was suggested for this substance by Weil and Stetten[20] who found that it was excreted in the urine

FAT SYNTHESIS IN THE BODY The body can synthesize fat from other building stones such as carbohydrate. For instance Brady and Gurin[7] showed that cell free preparations of pigeon liver synthesize fatty acids from labeled acetate To cite another example of this type of study and the complexity of metabolic processes it was found that, in liver slices, lipogenesis from C^{14} acetate was strikingly reduced by previous fasting or by a caloric restriction in the diet of the animals Refeeding after fasting or even a single administration of glucose enhanced fatty acid synthesis to a level higher than that found in the tissue of animals on ordinary diets

FAT CONTENT AND DIET PALATABILITY Whereas formerly many diets especially those for patients with liver disease contained little or almost no fat, it is now considered desirable to give at least enough fat to make it reasonably palatable and attractive to the patient otherwise the accompanying protein and carbohydrate calories will not be ingested and the entire objective of the diet defeated. Moreover there is evidence that a certain quantity of fat is required for normal growth. When certain unsaturated fatty acids are absent from the diet, animals may exhibit a marked retardation in growth and will develop skin lesions, histologic changes in many tissues, increased basal metabolic rates, and high water consumption, and even death may ensue Linoleic acid, of plant origin, and arachidonic acid, of animal origin, can prevent or cure these lesions[22]

Carbohydrates

The third major foodstuff, carbohydrate, has as its principal function that of supplying calories Yet in discussing it as a third separate foodstuff, one cannot but agree with Weinhouse[31] that "it is now recognized that the traditional division of metabolism into carbohydrate, lipid etc, is no longer entirely appropriate to modern biochemistry Not only have the broad fields become enlarged but they lose their identity at the intermediary stages with the formation of common metabolites"

As was stated above with regard to the formation of lipids from labeled acetate by the liver, it is now appreciated that the *acetyl group* represents the focal point for numerous dissimilative and synthetic processes. The progress of recent years in our understanding of how the major metabolic fuels glucose and fatty acid both yield this active intermediate has underscored the close metabolic interrelationships which exist between carbohydrate and fat. Thus, fatty acids may be formed from carbohydrate, and carbohydrate from fatty acids Certain hormonal influences are shown in Figure 32

CALORIC EQUIVALENTS In contrast to the approximately 4 cal which are derived from 1 gm. of protein or 1 gm. of carbohydrate, fat makes available approximately 9 cal per gm Absolute alcohol provides approximately 7 cal. per gm. or 6 cal per ml

Further Interrelationships Between Fat and Protein Metabolism

There is evidence that fats may have a specific regulatory effect on protein metabolism, this being over and above the protein

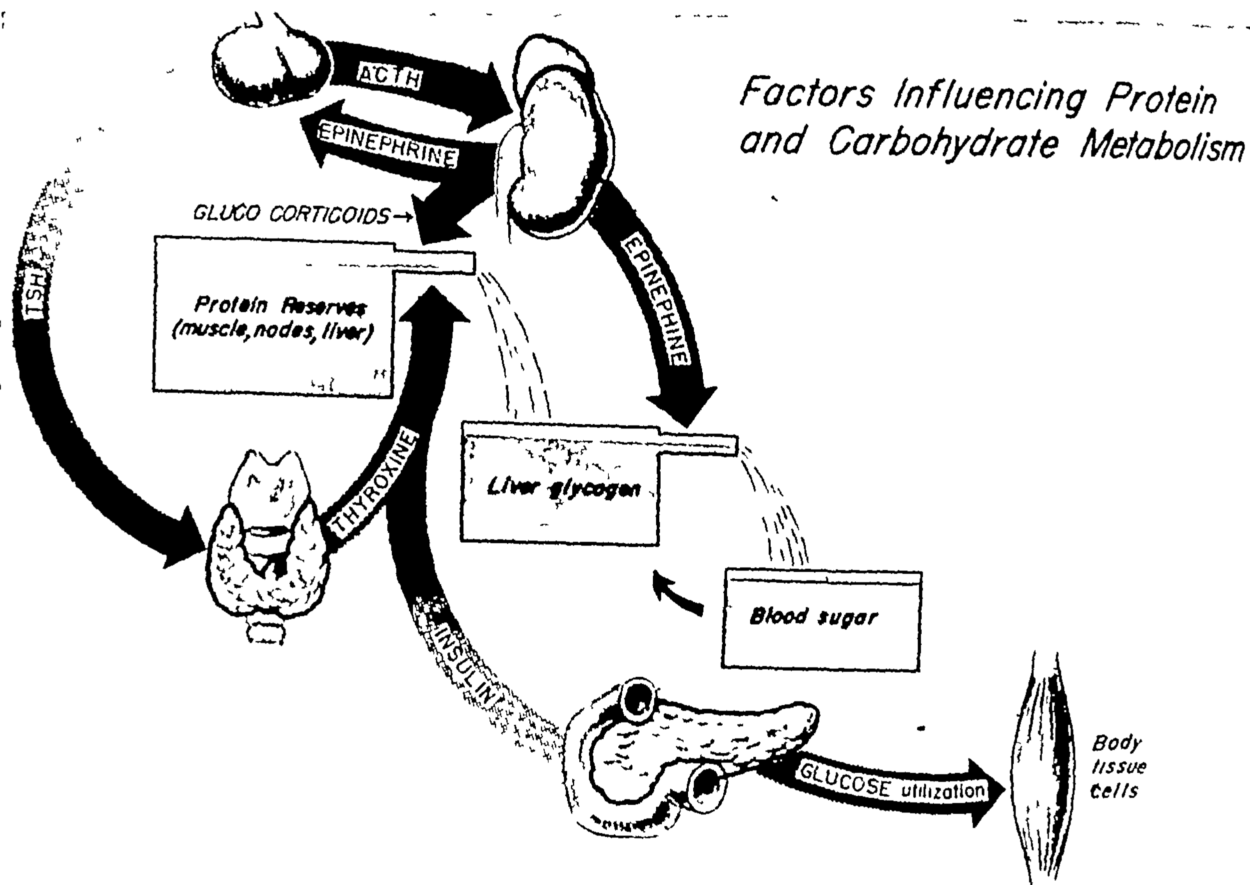


Fig 32 Glucose is the fuel which is most quickly required in stress It is derived largely from liver glycogen, glycogen, in turn, can be formed from glucose or from protein by gluconeogenesis (From HARDY, J D *Surgery and the Endocrine System* Philadelphia, W B Saunders Company, 1952)

sparing effect of the calories afforded by fat[13] It was found in animals and human beings that when fat constituted 30 per cent of the ration there was a decrease in the excretion of urinary nitrogen as compared with isocaloric rations containing 10 per cent and 20 per cent fat This was considered an indication that the nitrogen-sparing effect of fat was due, in part, to the higher fat content *per se* Moreover, animals consuming a low fat diet have been shown to excrete significantly larger quantities of certain amino acids in both the feces and the urine than animals eating a ration higher in fat[22]

CALORIC REQUIREMENTS—ADDITIONAL COMMENT As noted previously, the daily caloric requirement for the nonobese adult is from 25 to 30 cal per kg of body weight While the body can adapt to caloric restriction to some extent, after prolonged starvation or semistarvation the basal metabolic rate may decrease by 50 per cent, of this about two-thirds is due to shrinkage of the metabolizing mass of tissue and about one-third to a decrease in the intensity of the metabolism Nor is this reduction in energy expenditure explained by a reduced tissue temperature During starvation, complete or partial, there is a differential metabolic destruction of special tissues the brain, skeleton, and serum proteins remain fairly well intact for long periods, whereas fat, muscle, liver, and subcutaneous tissues undergo large losses The heart weight also decreases proportionately, but of course cardiac work is reduced during the period of deprivation

THE HAZARDS OF RE-ALIMENTATION The re-alimentation of semistarved individuals presents certain problems which are of much clinical importance. In brief, refeeding must be initiated gradually, lest diarrhea or even death occur This was forcefully impressed upon us when two patients, a man and a woman, in their eighties were admitted in a semistarved state Each had had for years a cervical esophageal diverticulum which rendered eating difficult, and during the

weeks immediately preceding hospitalization neither had consumed even a bare maintenance intake Each lived alone in a rooming house and thus, since it was difficult to eat under the best of circumstances, both were in a state of advanced starvation They were placed on a high caloric, high protein intake by means of a tube introduced at esophagoscopy The woman, however, developed diarrhea, and balance studies revealed that she retained only a small portion of the tube-fed calories and protein, the rest being lost in the stools She improved slowly the diverticulum was repaired under local anesthesia and she regained health The man, on the other hand, retained all the diet and died suddenly, approximately two days after the feeding had been started Autopsy revealed the effects of starvation but no particularly obvious probable cause of death. Unknown to us at the time, there are a number of reports in the literature that vigorous refeeding of the starved subject not infrequently results in sudden death presumably because the increased metabolic requirements imposed by the suddenly massive nutritional intake are more than the atrophic heart can bear, sudden heart failure being precipitated. Therefore it is advisable to begin re-alimentation with adequate protein but without an overabundance of calories. Incidentally, the systolic blood pressure of each of the two patients described above was usually in the eighties but this clearly did not represent "shock" in these subjects

Some Additional Factors in Nutritional Metabolism

So broad is the physiology of nutritional metabolism that certain aspects are discussed in several chapters of this volume In particular the effect of trauma upon the metabolism of protein fats, carbohydrates and electrolytes was discussed in Chapter 1

NONDIETARY FACTORS AFFECTING METABOLISM. Less food is required in warm climates than in cold climates troops stationed in the Arctic regions require up to 5000 cal or more per day, depending upon their activity [22] *Age* is also a factor, greater requirements being present during growth than after the person has reached adult stature As someone has remarked, children are in positive balance for almost everything except noise, the growth of children is similar to the gain in tissue which follows the wasting produced by a serious operation or other prolonged illness *Sex* is also a factor in nutritional requirements, for women often require fewer calories per unit of body weight than men, this may be a reflection of the relatively greater fat content of women The National Research Council recommends an average allowance of 60 gm of protein per day for women as contrasted to 70 gm. of protein per day for men [22]

As has been seen, *injury* and *disease* increase nutritional requirements, as do *pregnancy* and *lactation* Moreover, nutritional requirements are altered under circumstances of *psychological stress,* which include fatigue, tension and lack of sleep and climatic stresses. It has been noted elsewhere in this volume that diabetic ketosis and acidosis can be precipitated in well controlled diabetics with no change in their routine except the superimposition of severe emotional crisis This unquestionably reflects hormonal alterations

SURVEY OF ENDOCRINE INFLUENCES In brief, the anterior pituitary influences nutrition through elaboration of the growth hormone, adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), lactogenic hormone, and gonadotropins, with their manifold metabolic effects The *growth hormone* increases the need for amino acid building blocks by stimulating the growth of tissue Thus, growth hormone is apparently a protein anabolic factor which produces nitrogen retention. Purified growth hormones have also been found to have a nitrogen sparing effect accompanied in the fasting animal by an acceleration of fat metabolism.[23] It is well known that hypophysectomy causes profound alterations in the nutritional status of the individual Tes-

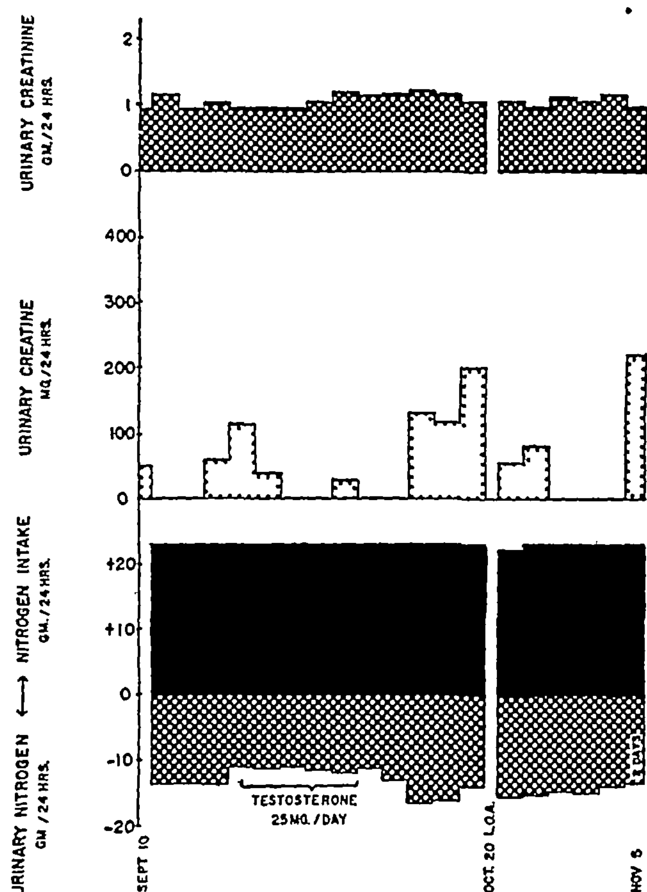


Fig 33 Effect of testosterone on nitrogen excretion This 23-year-old woman was placed on a constant caloric and nitrogenous intake for 10 days, and then testosterone was administered for 15 days During the period of hormonal therapy there was a definite increase in nitrogen retention, but this was reversed when testosterone was stopped (HARDY, J D Unpublished data)

tosterone produces nitrogen retention (Fig 33)

Special Nutritional Problems in Surgery

General Comment

The particular circumstance which often sets surgical patients apart from most other patients is the fact that operations upon the gastrointestinal tract preclude oral intake Not only may the patient come to operation in a much less than optimal nutritional condition, but it may be some time following the operation before he can eat—and intravenous nutrition is a poor substitute for oral nutrition

An additional cause of nutritional deficit is that which we often refer as "hospital starvation " By this is meant the scheduling of preoperative studies—in particular roentgenograms involving the gallbladder, stomach, and colon—on consecutive days with the purpose of getting the planned studies completed in the shortest possible time The preparation and the studies themselves may so interfere with food intake that the patient loses weight even preoperatively Even a well person would be weakened by missing most of his meals for several days, and this surely represents poor preoperative preparation for the patient

It is difficult to obtain objective data to support the view that hyperalimentation of the well nourished individual preceding operation, or the maintenance of positive nitrogen balance in the immediate postoperative period by massive tube feeding or intravenous therapy, improves surgical results Nevertheless, no one would seriously question the fact that a starved subject represents a less favorable operative risk than the well nourished subject In brief, we now feel that probably little is accomplished by producing a positive nitrogen balance during the first 72 hours postoperatively However, the less optimal the preoperative nutritional status of the individual, the more aggressively do we administer nutritive materials postoperatively

NUTRITIONAL STUDIES IN POSTOPERATIVE PATIENTS Numerous careful studies of the nitrogenous and caloric intake required to produce positive nitrogen balance following major operations have been reported In general, contrary to the older belief that positive nitrogen balance could not be produced in the immediate postoperative period, the various studies have, in many cases, demonstrated that a positive nitrogen balance can be achieved postoperatively provided that enough calories (even from 5000 to 6000) and large amounts of protein (from 2 to 3 gm per kg) are provided It must be understood that while positive balance is achieved, a tremendous loss of nitrogen in the urine occurs under these circumstances, partly due to the increased intake and partly due to the catabolic effect of the operation Again, there is no convincing evidence that

hyperalimentation in these patients during the first four days postoperatively provides any truly beneficial effect. It has been documented that postoperative nutritional alterations involve not only protein wastage with nitrogen excretion, but also a decreased carbohydrate tolerance (increased insulin resistance), and the combustion of considerable amounts of fat. A number of pertinent factors are shown in Table 3.

Nutrition Following Gastric Resection

The nutritional complications which may follow gastric resection have appropriately been reviewed in some detail in connection with the physiology of the stomach. Nevertheless, it is of value to mention here that the nutritional difficulties which follow high or total gastric resection are, along with the problems attending the management of a small bowel fistula, perhaps among the most difficult with which the surgeon must deal. There is now a trend away from extremely radical gastric resections for benign duodenal and gastric ulcers, to a less radical procedure in which less of the stomach is removed, perhaps in combination with vagotomy. Furthermore, it appears that nutrition may be more readily maintained following the Billroth I or the vagotomy gastroenterostomy procedure than following a Billroth II procedure.

In general, the difficulties in maintaining weight and nutrition in patients who have had a high gastric resection are largely due to excessive "dumping" or to the fear that the symptoms of dumping will occur if the patient eats, or to too rapid transit of the food materials through the small bowel (essentially a variant of the dumping syndrome)—and not necessarily to defective small bowel absorption *per se*. Yet, a number of studies appear to show that when the food is made to pass through the duodenum and presumably is mixed with the digestive juices in the usual way, as occurs after the Billroth I procedure, weight is more readily maintained than after the Billroth II operation. This advantage is often due

TABLE 3. SOME FACTORS THAT INFLUENCE NUTRITIONAL REQUIREMENTS AND SUCCESS

1. Previous nutritional condition
2. Age
3. Sex
4. Trauma
5. Infection
6. Exercise
7. Metabolic rate
8. Presence of excessive losses (suppuration, fistula, diarrhea)
9. Composition and balance of food intake
10. Malignant tumors
11. Hormonal imbalance as in Cushing's syndrome or diabetes mellitus

to a decreased loss of fat and calories in the stool, so that the absorptive factor *per se* cannot be disregarded as a cause of weight loss following gastric resection.

Routes and Materials for Therapeutic Alimentation

ORAL. There can be no question whatever that whole food introduced by the oral route is more beneficial to the patient than the split products that can be administered intravenously. A gastrostomy is superior to a jejunostomy for feeding purposes, but both are less effective than the oral route. Moreover, even when food is introduced by the oral route the nutritional effect of whole protein appears to be better than that achieved by the administration of split protein products (Fig. 31). Why, one might ask, is it necessary to consider the oral route at all since, presumably, if it is available the patient could and should eat of his own accord?

To begin with, the patient may be in a condition which, were he *to be allowed* to eat unlimited quantities of food, might result in severe metabolic difficulties, particularly if he has previously been starved for some time. Second, while the oral route may be available, the patient may not desire to consume the food, as in patients with anorexia nervosa and in numerous other conditions. Similar though less profound psychologic deterrents to adequate nutritional

intake are found among many preoperative and postoperative surgical patients In such subjects it may become desirable to pass a small polyethylene nasogastric tube for liquid alimentation If the high caloric feeding mixture is too thick, gravity alone may not be adequate and some type of pump must be used to avoid plugging of the small tube

Or, the patient may wish to eat but is prevented from doing so by an esophageal carcinoma or diverticulum In such a situation it is, again, a common practice in our clinic to use esophagoscopy and, if possible, to pass a small tube into the stomach for

TABLE 4 Intravenous Alimentation

A Caloric values of foodstuffs	
Carbohydrate (CHO) (glucose, fructose)	4 cal /gm
Protein (or protein hydrolysate)	4 cal /gm
Fat	9 cal /gm
Alcohol	7 cal /gm
B Daily requirements (minimal)	
Calories	25/kg body weight
Protein	1 5 gm /kg body weight
C Add vitamins, especially C	
D Intravenous feeding	
1000 cc 5% glucose (50 gm CHO)	200 cal
1000 cc 10% glucose (100 gm CHO)	400 cal
1000 cc protein hydrolysate-glucose mixture (5% each)	400 cal
70 grams of alcohol (7 cal / gm)	490 cal

In general, only 1 L of fluid containing alcohol and 2 containing protein hydrolysate are well tolerated over one 24-hour period

feeding purposes. Much nutritional provement can often be achieved preo atively in the patient with carcinoma of esophagus, since the wasting which he hibits may have resulted more from an ability to take in food than to the pecu inability of the cancer patient to utilize gested food in the more advanced stage his disease

There has been an increasing tendenc utilize oral fat emulsions to provide ab dant calories, as fat provides approxima 9 cal per gm However, the oral fat prepa tions on the market (*e g* , Lipomul, Upjo are usually diluted and may provide c approximately 4 cal per ml Moreover, tl is a limit to the number of fat calories wl can be tolerated by the individual, a co mon upper limit being in the neighborh of 2200 cal per day for fat administe orally, if greater than this amount is gi gastrointestinal symptoms may develop

Caloric values of common foodstuffs given in Tables 4 and 5

TABLE 5 Adverse Effects of Obesity Surgical Patients

1 Pulmonary ventilation is hampered by ward displacement of diaphragm
2 Inhalation anesthetic agents are usually sorbed in greater amounts
3 Cardiovascular reserve is often impai hypertension is more frequent
4 Liver functional reserve is impaired by fa infiltration
5 Diabetes is more common, to complicate c valescence
6 The exposure at operation is more diffic (the fat in the omentum and mesentery n be as voluminous as that in the abdomi wall)
7 Poor water and blood flow through the fat the abdominal wall reduces the inflow leukocytes, antibodies, and antibiotics, tl plus a marked tendency to necrosis of fragile fat cells, results in an increased in dence of wound infection and wound disr tion
8 It is more difficult to estimate drug and fl requirements safely on a weight basis (p 29) when the patient is fat

A formula which is useful for oral tube feeding is as follows

Homogenized milk	500 ml
Gevral Protein (Lederle)	175 gm
Cartose (glucose)	300 gm.
Klim (powdered whole milk)	75 gm.
Raw eggs	4
Water to bring to total volume of	1000 ml.

This formula provides about 21 gm. of nitrogen (130 gm of protein) per L. and is low in fat. With this preparation it has been possible to give an occasional patient up to 6000 cal. per day Diarrhea, the most troublesome complication of tube feeding, can usually be successfully managed by introducing the feeding into the stomach at a slow rate (1–1 9 ml per minute) Yet, at a slow rate it is necessary, as noted above, to use some form of mechanical feeding pump to prevent plugging of the tube by the thick formula With this formula it has been necessary in some patients to include with each feeding 100 mg of Banthine and variable amounts of paregoric during the first 48 to 72 hrs to inhibit intestinal motility After the first two or three days it has usually been feasible to discontinue these agents and no further diarrhea has resulted. In patients whose physiologic state can tolerate the high caloric high protein diet provided in this mixture it may be possible to increase the patient's weight by as much as 1 lb per day for several weeks Total body water measurements combined with nitrogen balance studies will indicate the water content and often the type of the tissue being laid down The prompt improvement in the patient's psychologic outlook following a period of hyperalimentation by tube feeding is frequently most gratifying emphasizing the close relationship which exists between nutritional adequacy and mood

GASTROSTOMY FEEDING While the use of the polyethylene tube may render preoperative gastrostomy unnecessary there are many circumstances under which diseases of the esophagus or mouth preclude oral tube feeding and a gastrostomy must be done. In general, the simple and easily performed Stamm gastrostomy is about as satisfactory as the other more complicated procedures Too, it is readily taken down in the event one wishes to pull the stomach into the chest to be anastomosed to the esophagus, or when the gastrostomy is no longer needed

Skimmed milk may be used as a basic ingredient of many gastrostomy formulas, other materials being added gradually as tolerated

Whole foods may be homogenized with a Waring blendor or other means and fed through the nasogastric tube

JEJUNOSTOMY FEEDING We have not had a large experience with jejunostomy, but we do not hesitate to use it when it appears to be the only means available for maintaining life Nevertheless, the experience that we have had with this route of feeding patients has been one of rather limited success For one thing it has usually been employed only after the patient was in the most dire nutritional circumstances Second, occasional complications due to the technic itself have occurred In one patient, the #16 French rubber catheter (introduced approximately 3 in. into the distal jejunal loop and Witzeled in) impinged on the wall of the bowel when postoperative inflammatory adhesions produced a sharp kink in the loop, and eventually the tube eroded through into the free peritoneal cavity with fatal peritonitis

In contrast, Zollinger and his associates,[33] who have had a relatively large experience with jejunostomy performed often under optimal conditions reported that in approximately one-half their cases the jejunostomies were considered to have been definitely worthwhile They felt that the general condition of the "successful" patient was definitely improved, and that in some cases the jejunostomy feeding had been life-saving

The incidence of gastrointestinal complications—nausea, vomiting or diarrhea—is considerably greater in patients fed by je

junostomy than in those fed by gastrostomy or by the oral route Moreover, with jejunostomy the material must be introduced at a much slower rate (keeping the patient immobilized while the material drips in) if loose stools are not to result Consequently, it is more difficult to achieve a satisfactory nutritional intake with jejunostomy than with gastrostomy Again, skimmed or homogenized milk is a useful basic ingredient to use in the formula, supplemented progressively with other materials There has been little difference in the incidence of diarrhea with homogenized as compared with skimmed milk Zollinger and Ellison[34] employ homogenized milk, which contains approximately 700 cal and 35 gm of protein per L They find that most patients will take as much as 2400 ml per day, and in this way 84 gm of protein and 1680 calories are provided

INTRAVENOUS ALIMENTATION In the overwhelming majority of patients who cannot eat, the intravenous route is employed, at least temporarily, in achieving what nutritional intake can be given by this means Intravenous alimentation is conveniently used for relatively short periods of time, and it usually is sufficient to tide the patient over the immediate preoperative or postoperative emergency Moreover, at this writing a woman has just been discharged, cured of her gastric fistula after four months of almost constant intravenous alimentation To re-emphasize, though, for caloric maintenance over prolonged periods the oral route is by any comparison the best, gastrostomy next, jejunostomy perhaps next and the intravenous route last

During recent years it has become possible to give greater amounts of calories by vein than had previously been possible In addition to the use of hypertonic solutions of *glucose*, *alcohol* (6 to 7 cal per ml), and *fructose* (4 calories per gm.), *intravenous fat mixtures* have quickened interest in the feasibility of truly adequate parenteral alimentation In our clinic intravenous fat is now rather frequently used in debilitated patients, with beneficial effect and relatively few reactions Since fat contains 9 cal per gm , a fat mixture, even if diluted as it must be for intravenous infusion, still offers a means of introducing a considerable number of calories As stated, fat has usually been given in approximately 15 per cent concentration, which affords approximately 900 cal per L Massive amounts are unsafe

Finally, *protein hydrolysates* have been widely used for a number of years to provide nitrogenous intake However, our own results, as well as the studies of many others, have demonstrated that amino acid mixtures are nutritionally inferior to whole protein mixtures

The usual liter of amino acid or protein hydrolysate contains from 40 to 50 gm of split protein products in a 5 per cent (50 gm) glucose solution By increasing the glucose solution to 10 per cent, an additional 200 cal can be made available (200 from the 50 gm of protein products, and 400 from the 10 per cent glucose) If to this solution one adds 70 ml of absolute alcohol, allowing some loss for the necessity of removing a portion of the fluid in the bottle to permit the introduction of the alcohol, he then provides in this liter of fluid an additional 490 cal Thus, by the administration of 1 L of protein hydrolysate solution in 10 per cent glucose and 70 ml of absolute alcohol, one can theoretically provide the patient with approximately 1000 cal and 50 gm of split protein products The administration of 2 L of this solution during the 24-hr period affords an intake of 100 gm of protein products and approximately 2000 cal Nevertheless, these values are all approximate, and upon chemical analysis one will find that the stated constituents of protein hydrolysate preparations vary between brands and even in the product from the same company at different times Therefore, if one wishes to do accurate nitrogen balance studies using intravenous protein hydrolysate solutions, he is obliged to run a nitrogen analysis on each liter of fluid infused to achieve valid studies Moreover

it might be mentioned here that the electrolyte content also varies considerably The usual protein hydrolysate solution is low in sodium and low in potassium, but since some companies employ an alkali for hydrolysis, the solution may contain a disproportionate amount of sodium as compared with fixed anions such as chloride

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Chapter 4

The Physiology of Connective Tissue, Wound Healing, and Homotransplantation of Tissues

Physiology of Loose Areolar Connective Tissue: A Few Notes

Since wound healing consists in such a large measure of repair by means of connective tissue, it is pertinent to examine certain aspects of the physiology of such tissue The review by Ragan[35] has been drawn upon freely in the following discussion

The main *functions* of loose areolar connective tissue are. (1) support, (2) transport, (3) storage, (4) repair (healing), and (5) protection (antibody formation) Another possible function which has been ascribed to this tissue is that of assisting in the regulation of salt and water metabolism, but this remains to be proved

The three major *components* of connective tissue are the *amorphous ground substance*, *fibrillar elements* (reticulum, collagen, and elastic fibers), and *cells* (fibroblasts)

Connective tissue is developed from embryonal mesenchyme It is generally accepted that in the development from embryonal to adult tissue the macrophages, mast cells, fibroblasts and endothelial cells (which evolve into capillaries and larger vessels) are derived from stellate mesenchymal cells Ground substance is believed to be derived during embryonal development from the embryonal syncytium

Ground Substance

In adult tissue, ground substance may b secreted by fibroblasts or by mast cells fro an heparin-like precursor. The secretion c ground substance is probably mediated b vitamin C, since in scurvy very little meta chromatic material is present in regeneratin connective tissue Mast cells have also bee said to secrete the hyaluronic acid of syno vial fluid, and synovial cells grown in tissu culture have produced a "mucin " There ar those who believe that the ground substanc may vary in a reversible manner from a rigid gel to a more or less fluid state, depending chiefly on the rate of replacement of glycoprotein and on the degree of depolymerization of the glycoprotein caused by enzymes of the mucinase class In support of this possibility, it has been shown that the glycoprotein of the ground substance in mice becomes more highly polymerized at about the time of birth, this polymerization being greatest at the site of formation of the basement membrane The younger material is water soluble, but with maturation it becomes insoluble and more highly polymerized

Continuing with the ground substance, three types of chondroitin-sulfuric acid (a mucopolysaccharide), all varying in specific rotation and in enzymatic reaction, have been isolated from various sources It has

been estimated that in 100 gm of fresh human skin there are approximately 24 5 mg. of hyaluronic acid and 26.2 mg of chondroitin sulfuric acid The enzyme hyaluronidase hydrolyzes hyaluronic acid and certain chondroitin sulfates

Histologically, in repair a progressive series of changes have been found to occur in areolar connective tissue, with a shift from the amorphous to the fibrous elements of the intercellular substances

In essence Ragan points out that the origin of the ground substance is not clearly defined, that its turnover if any, is not known that its function is still a matter of conjecture

Fibrillar Elements

RETICULUM AND COLLAGEN It has been shown that *fibroblasts are essential for the production of collagen fibers* and in tissue culture fibrin fibrils bear no special relation to the deposition of collagen Fibrin itself is a fibrous protein, and it has a characteristic electron microscopic structure Fibrils join laterally to form compound fibers, depending on the pH, and clotting has been represented as three-dimensional polymerization It has been suggested that collagen is formed by an enzyme present in the ground substance from a soluble polypeptide derived from the fibroblast.

By means of electron microscopy (Fig. 34) it has been seen in tissue cultures of fibroblasts that a precollagen consisting of nodular filaments and some larger, finely striated fibrils are present, it is believed that these represent a stage in the extracellular development of collagen. The smallest collagen filaments consist of chains of globular protein molecules The unit fibers or component units of collagen then come together into parallel arrays in a manner similar to that in which the unit fibers of fibrin aggregate to produce large strands of a clot.

Porter[34] was able to demonstrate that the early collagen fibril is apparently spun off the surface of the fibroblast. He believed



Fig 34 Electron microscope photograph of collagen fibers (Courtesy of Dr C A Ashley of the Walter Reed Hospital Washington D C, and Dr K R Porter of the Rockefeller Institute of New York)

that the material for the fibril was derived from the plasma gel of the fibroblast and also possibly from fibroglial fibers He found that the smallest fibril, as spun off the surface of the fibroblast, had a periodicity of 210 Å After the fibril had been spun off the cell and while it was lying in the extracellular space, every third period seemed to enlarge and the typical collagen spacing of 640 Å developed

Collagen which has been produced in tissue culture, was thought by Hass and McDonald[13] to be a secretory product of fibroblasts New collagen is not laid down unless fibroblasts undergo proliferation. Lymphocytes appear to take no part in collagen deposition

Collagen (Fig 34) has little elasticity but great mechanical strength is insoluble in organic solvents, water, dilute acids, and alkalies at ordinary temperature but has a large swelling capacity in aqueous acids or alkalies in the absence of a high salt concentration When collagen is heated sufficiently it is converted into gelatin Collagen is not attacked by trypsin, but can be di

gested by pepsin at a low pH, since under such conditions the native fiber is disrupted However, trypsin does hydrolyze gelatin Collagen is, of course, quite susceptible to the action of the enzyme collagenase, and 0 1 mg of collagenase will often liquefy 25 mg. of collagen

ELASTIC FIBERS This third major fibrous element of connective tissue (the other two being reticulum and collagen) appears late in embryonal life Although the cellular source of elastic fibers is as yet unknown, in tissue culture these fibers are produced only by tissues which contain them *in vivo*

Elastic fibers are capable of great mechanical strength and long range elasticity They are resistant to boiling water, dilute acids, and alkalies These are not susceptible to recrystallized trypsin but are hydrolyzed by a crude pancreatic enzyme which has been called "elastase" Upon exposure of elastic fibers to a preparation of elastase, an opalescent solution appears which separates into a clear solution and a creamy fraction This creamy fraction consists of sphingomyelin, lecithin, cholesterol, and cephalin

Ragan summarized the foregoing essentially as follows It would appear that fibroblasts develop from stellate mesenchymal cells and deposit ground substance, then spin reticulum The reticulum associates laterally into collagen, losing its argyrophilia in the process, with orientation of cells and fibers in accord with mechanical stresses The origin of the elastic fiber is unknown Functionally, the fibrous and amorphous elements serve their purpose well· *Reticulum* acts as a fine meshwork surrounding and serving as a supporting structure for organs and blood vessels, *collagen* provides a fiber of great mechanical strength for cohesiveness, *elastic fibers* permit long range elasticity for movement and rebound The *ground substance* acts as a medium for transport and for storage of water and electrolytes and with its gel-like character, also absorbs shocks Teleologically, an excellent adaptive mechanism for simple support and transport would appear to have b... evolved

The Dynamic State of Connective Tis...

Although the concept of the dynamic st... of the living organism has largely repla... the idea that the structures of the li... organism were more or less static in nat... relatively little information is available... garding the molecular turnover in sim... connective tissue However, from calc... tions based on excretion studies and N^{15} corporation into body protein, the half-... of proteins of carcass tissues appears to... quite long

The Healing of Wounds

The healing of an incision is such a co... monplace thing that the student rarely... cords this process the importance it deser... Nevertheless, if the trainee follows eno... wounds from incision to white scar to kn... the natural history of the healing and... complications, he will have learned a gr... deal about the practice of surgery

Histophysiology

One of the major functions of the co... nective tissue is that of the repair of woun... following trauma or following injury fr... infections and other noxious agents Regar... less of the type of injury, the host respo... is basically similar

Following accidental injury or an opei... tive incision, a substance is elaborated in t... damaged tissue which Menkin[26] term... "leukotaxine" This material appears to i... crease capillary permeability and, with t... increase, polymorphonuclear leukocyt... lymphocytes, and monocytes migrate in... the area of injury At the same time, so... substance is present which causes the leuk... cytes of the blood stream to adhere to t... capillary wall, and gradually these leuk... cytes pass through the wall and into t... damaged tissue Fibrin is laid down in t... area and shortly thereafter fibroblasts a... pear, following their appearance, groun...

substance can be demonstrated by histochemical technics

As reticular and collagenous fibers develop, new blood vessels grow out from capillary buds on pre-existing vessels The pH at first decreases and becomes more acid but then returns to normal as the reparative process continues toward the normal state It is of interest that a decrease in pH has also been found at the site of fractures in the first stage of the reparative process The biologic factors which initially promote these processes that eventually result in wound healing—and the biologic controls which effect a cessation of the proliferative activity of the various tissue elements of the wound once healing is complete—are unknown

The Stages of Wound Healing[16]

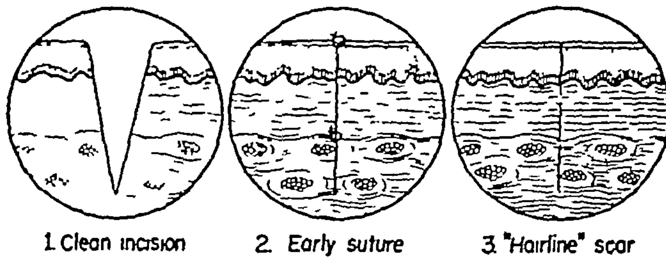
FIRST STAGE EXUDATIVE OR LAG PHASE Following a simple incision which heals uneventfully there is first the escape of blood serum and lymph which form the coagulum a dense fibrin network which is filled mainly with erythrocytes and leukocytes This coagulum serves as a scaffolding which temporarily unites the edges of the wound, it also serves later as a bridge for the ingrowth of fibroblasts. Soon after the injury phagocytes appear and remove devitalized tissue while all leukocytes serve as protection against bacterial invasion. The enzymes of the wound which were studied by Howes and others[15] doubtless have to do with the digestion of necrotic material and with promoting other phases of wound toilet and healing New blood vessels may begin budding as early as the third day but even so during the first four to five days the wound is dependent largely upon the union afforded by the fibrinous exudate and the tensile strength of this is very low thus, during this exudative or lag phase the strength of the wound is largely dependent upon the suture material that was used for closure

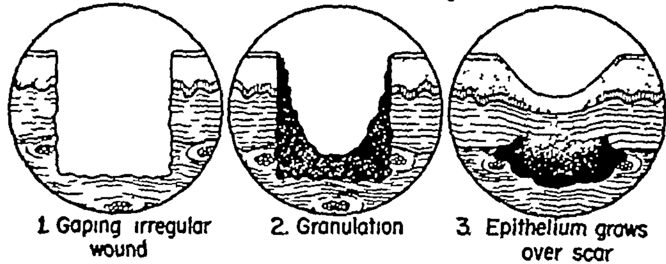
SECOND STAGE FIBROPLASIA. Following the lag period which lasts four or five days the second phase of wound healing begins This is the stage of fibroblastic proliferation or fibroplasia The strength of the wound during this time is not as great as that afforded by the sutures immediately after repair, for the actual tensile strength of the wound is minimal and the holding power of the tissues for sutures drops progressively Stage two lasts from about the fifth postoperative day to the fourteenth or sixteenth day, by which time the wound has achieved the maximum strength afforded by the connective tissue scar, as a rule It is during the early part of stage two, when absorbable sutures are weakening but fibroblastic union is still minimal that wound complications are most likely to develop

THIRD STAGE MATURATION Certain structures such as bone, tendon and fascia have in effect, a third stage of wound healing a stage during which maturation or differentiation is occurring for greater strength is required in these tissues There may be some lag between the second and the third stage, and this differentiating process by which the original strength of the tissue is regained may last for many months Indeed it is well known that progressive realignment of the united fracture may continue for several years.

Connective tissue *per se* may have, in effect a third stage of healing which may be called the *phase of contraction* during which the line of incision is assuming first the dull red appearance of the early scar, followed over the months by an increasing contracture and whitening During this phase the scar tissue becomes more compact and less cellular, and the vascular branches are squeezed until many of them are obliterated Occasionally the phase of fibroplasia is not terminated in the usual period of time and the proliferating fibroblasts continue to reproduce until a *keloid* is formed

Keloids may prove most difficult to manage for the excision of one is usually followed by the formation of another at the same site Neither cortisone therapy nor x ray has controlled this tendency satisfac





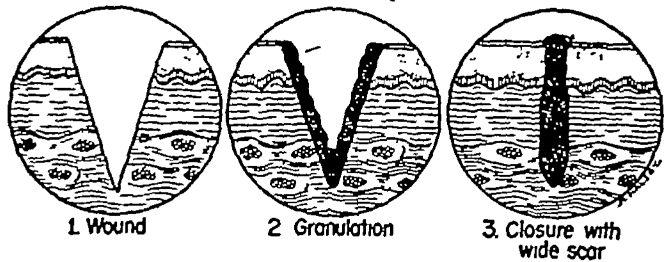


Fig 35 Types of wound healing ("Chronologic course of wound healing by first, second and third intention In the final stage of second intention healing it is to be noted that the underside of the epithelium is smooth and not serrated as normally In the third stage of third intention healing an early phase is shown Later the granulation tissue will be incorporated as a wide fibrous scar" HARKINS, H N In *Surgery—Principles and Practice*, edited by Allen, J G, Harkins, H N, Moyer, C A, and Rhoads, J E, Philadelphia, J B Lippincott Company, 1957)

torily Occasionally a fibrosarcoma may arise in a keloid

Healing by First Intention, Delayed Primary Closure, Healing by Second Intention, and Healing by Third Intention or Secondary Suture

The terminology of wound closure (Fig 35) has been a source of much confusion *First intention* (primary union) is the term used when the wound is sutured at once and heals without event *Delayed primary closure* is not to be confused with the term of "secondary suture," since delayed primary suture simply means that the wound is allowed to remain open for perhaps four days and then closed as usual Healing by *second intention* (granulation) is referred to as the situation which exists when the wound is allowed to "granulate in", the skin heals by contracture, with gradual diminution of the size of the skin defect by scar formation Healing by *third intention* or *secondary suture* is that healing which occurs when, after perhaps several weeks, the edges of the unhealed wound are undermined and freshened and the defect brought together with sutures to hasten the rate of healing

To avoid misunderstanding, it is recommended that the student know what he is talking about and describe it, rather than to go through the laborious procedure of memorizing the various terminologies for the types of wound healing under discussion

The Healing of Individual Tissues

SKIN Healing of the skin may be very rapid and, if the cut edges of a wound are closely approximated, epithelial repair *per se* may be far advanced by the end of from 48 to 72 hours Indeed, it is stated that evidence of epithelial cell migration may be noted sometimes within an hour after trauma As a general rule, however, skin sutures are removed from wounds about the face and neck (if a buried, subcuticular stitch has not been used) by the end of from 48 to 72 hours, and from most abdominal incisions by the end of five days Yet, in contrast, it is well to leave sutures in incisions involving the back or shoulder for from six to eight days or longer (Fig 36) since the stresses of movement may result in disruption of the wound with an unsightly cosmetic result

FASCIA Rates of fascial healing are shown in Figure 37

MUSCLE Muscle cells do not take part in the active process of tissue regeneration, for muscle defects are repaired with fibrous scar tissue For this reason damaged muscle tissue should be removed, since it will not regenerate and heal and, rather than assist in the union of the wound, will act as a foreign body and furnish a culture medium for bacteria For this same reason—and it applies in the correction of diastasis recti—there i

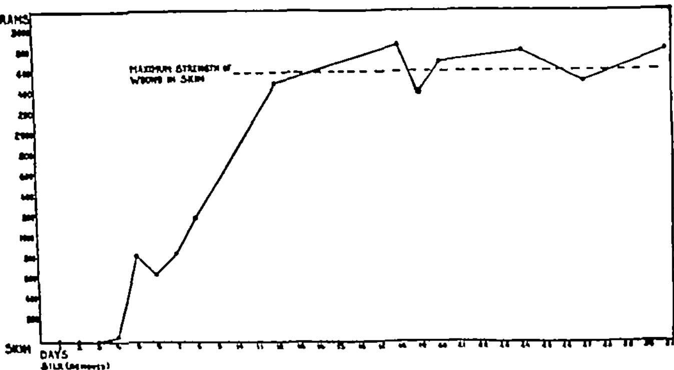


Fig 36 Wound healing curve for skin Note that a moderate increase in tensile strength occurred between the fourth and fifth days, and that thereafter the tensile strength increased rapidly up to about the eleventh day (From Howes E. L., Sooy J W., and Harvey S C The healing of wounds as determined by their tensile strength J A M A 92: 42 1929)

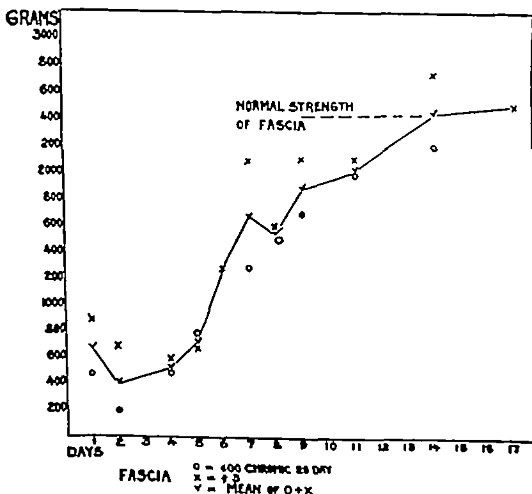


Fig 37 Wound healing curve for fascia Note that the wound begins to gain strength after 5 days and reaches normal strength by the end of about 14 days (From Howes E L., Sooy J W and Harvey S C The healing of wounds as determined by their tensile strength J A M A, 92: 42 1929)

no point in using heavy suture material to suture muscle bundles together It is enough merely to bring them together loosely, else the sutures will cut through

TENDON After a lag period of from four to five days, the fibroblasts proliferate This fibroblastic tissue later becomes rather avascular and the connective tissue fibers become arranged longitudinally in the lines of stress, as is characteristic of normal connective tissue Short gaps between the tendon ends may be bridged by tendon cells within two weeks but, more often, solid union is not achieved until a longer period has elapsed Mason and Allen[25] demonstrated a decline in tensile strength of sutured tendons during the first five days after injury, but this was followed by a rapid increase in strength which reached a plateau on about the sixteenth day. From the nineteenth to the twenty-first day there was a further increase in tensile strength of the tendon He recommended that passive movement of the repaired tendon be started two weeks after injury, not only to increase the tensile strength of the tendon but also to diminish the likelihood of immobilization of the tendon by adhesions Active movement is begun gradually at approximately three weeks

BONE The initial processes of bone healing are much the same as for soft tissue healing, but soon the proliferation of the connective tissue occurs from the endosteum, the periosteum, and the Haversian canals Osteoblasts from the periosteum and endosteum form fibrils which extend in all directions and these fibrils, as well as the cells themselves, become embedded in an homogeneous matrix Calcium salts are deposited in this matrix, and callus is then said to be present Further callus formation and some absorption occurs, and gradually the new bone takes on the characteristic pattern Excess callus is usually produced, but this is gradually revised by reabsorption and over the ensuing months the normal contour of the bone is restored

The elements of bone have been shown to be in constant turnover, and following fracture the increased amounts of calci[illegible] excreted are derived not only from the s[illegible] of the fracture but from other bones as w[illegible]

NERVE Section of a peripheral nerve r[illegible]sults in the well known process of Waller[illegible] degeneration, in which the nerve axons [illegible] fibrils break into granular fragments T[illegible] myelin sheaths undergo chemical chang[illegible] to form irregular fatty globules in the ti[illegible]sues and, finally, the degenerated fibrils an[illegible] myelin are absorbed The cells of the ner[illegible] sheath, on the other hand, proliferate a[illegible] result in a new sheath which acts as a r[illegible]ceptacle or strut for the regenerating fun[illegible]tional nerve ends It is frequently diffic[illegible] to state categorically in the given patie[illegible] whether or not regeneration of a peripher[illegible] nerve has reached its maximum or will co[illegible]tinue further After three months, howeve[illegible] the chances of regeneration of addition[illegible] peripheral nerve fibers diminish rapidly, [illegible] part because of the increasing denseness [illegible] the surrounding scar tissue Unless imme[illegible]diate nerve suture is performed within s[illegible] to eight hours following injury, it is the com[illegible]mon practice to allow from six weeks t[illegible] three months for the inflammatory reactio[illegible] to subside, before re-exploring the area. In[illegible]cidentally, it is helpful to tag the nerve end[illegible] with a black silk suture at the initial clo[illegible]sure It has been estimated that the re[illegible]generating nerve may advance peripherall[illegible] at a rate of approximately one millimeter o[illegible] more per day

GASTROINTESTINAL TRACT Healing of anas[illegible]tomoses in the alimentary tract, particularl[illegible] as regards the epithelium of the mucosa[illegible] proceeds at the same rapid rate as does th[illegible] healing of the skin As shown by Antoin[illegible] Lembert, a pupil of Dupuytren's, it is es[illegible]sential that the sutures be so placed tha[illegible] serosa is in contact with serosa. If mucos[illegible] protrudes through the suture line, a fistul[illegible] will often result For satisfactory healing[illegible] the blood supply must be adequate, this i[illegible] always a hazard in esophageal surgery bu[illegible] rarely so in gastric surgery.

Local Factors Which Influence Wound Healing

ARTERIAL SUPPLY As just stated, a most important factor for the proper healing of any type of wound is the arterial blood supply If the blood supply is inadequate, the tissue edges will become necrotic and will not hold the suture material A frequent cause of inadequate blood supply to the healing wound edges is that the wound was closed under too much tension, resulting in occlusion of the finer vessels

FOREIGN MATERIAL (Fig. 38) The use of excessive amounts of suture material is inimical to good wound healing Furthermore, the formation of an hematoma in the wound further forces the healing tisues apart and diminishes the rate of wound healing This hematoma must either be removed by macrophages, by liquefaction and absorption, or by drainage to the outside In all too many instances the hematoma is not absorbed and must drain spontaneously or be drained surgically

INFECTION A third important factor in the healing of a wound is whether or not the wound becomes infected Infection results in destruction of the healing fibers of the wound, and it also interferes with the blood supply by occluding the finer vessels In addition collections of pus act mechanically as foreign material and must be evacuated or absorbed before proper wound healing will take place Gastrointestinal procedures in obese patients are particularly prone to result in infection in the subcutaneous fat. When infection does occur, it is far more desirable to have the pus drained to the outside than to have the infection proceed in the opposite direction and result in a separation of the fascial layers, which tissue represents the true strength of the healed wound In fat individuals it is frequently advisable to place subcutaneous drains and to close the skin loosely around them, especially in situations where contamination of subcutaneous fat may have occurred. Among such operations are colon resection employing an open anastomosis (which I prefer), the removal of a suppurative or ruptured appendix and the repair of a ventral hernia in a fat person regardless of whether bowel was opened or



Fig 38 Gunshot wound of anterior thorax and arm Initial drainage was inadequate and further surgery was required When the wound was again explored and debrided the upper components shown were removed The entire defect was then grafted There developed a late contracture of the grafted axillary extension of the wound and this was freed by a Z-plasty

not Fat is quite fragile, and the mere retraction of fat may be sufficient to cause disintegration of a certain number of fat cells with the liberation of an oily material which must find egress from the wound Many wounds are considered to be infected following the repair of a ventral or umbilical hernia in an obese person when, in fact, the "pus" is not significantly contaminated with bacteria but represents chiefly the drainage of the oily material liberated by the liquefaction of subcutaneous fat The chief function of the drains is to prevent the accumulation of serum, blood, or purulent material in a "dead space" within the healing wound, such an accumulation increases the morbidity, impairs cosmetic success, prolongs the hospital stay, and upsets the patie[nt] (and the referring physician)



Fig 39 Obesity and wound healing There was poor healing of this incision through an obese abdominal wall, and the lower portion of the wound separated down to the fascia Had the fascia too separated (but not the peritoneum) a hernia might have later developed Had the peritoneum also separated, evisceration might have occurred Actually, it was a simple matter to reapproximate the skin edges, and satisfactory healing was achieved

The reason why fat so readily become[s] infected is, again, that its low blood suppl[y] and water content result in facile necrosi[s], in diminished local tissue protection by anti[-]bodies and leukocytes, and in reduced pene[-]tration by antibiotics (Fig 39)

General Factors in Wound Healing

PROTEIN INTAKE In 1938 it was demon[-]strated by Thompson, Ravdin, and Frank[4] that wound healing was retarded in the pres[-]ence of a significant hypoproteinemia Sinc[e] that time it has been generally acknowledge[d] that the body protein reserves have muc[h] to do with the healing of wounds, and clini[-]cally and experimentally it has been re[-]peatedly shown that wound healing is no[t] optimal when the plasma protein levels ar[e] low

VITAMIN INTAKE Ascorbic acid (vitamin C) deficiency results in retarded wound healing and, according to recent evidence, it may also cause degenerative changes in previously healed wounds In Anson's voyage in 1769 it was recorded that "the scars of wounds which had been for many years healed were forced open by this virulent distemper" (scurvy) Experimental support of this presumptive susceptibility of scar tissue to vitamin C deficiency was reported by Pirani and Levenson[33] They first reared guinea pigs on a diet containing adequate amounts of ascorbic acid A linear midline laparotomy incision 4 cm in length was then performed on each animal and the wounds were allowed to heal for six weeks At the end of this time half of the animals were placed on a diet free of vitamin C and the other half were given a nutritionally complete diet to serve as controls Signs of scurvy developed in the "deficient" animals by the seventeenth or eighteenth day and were pronounced by the twenty-sixth day At this time considerable swelling, herniation, and hemorrhage were noted in the laparotomy scars of the "deficient" animals

No similar changes were noted in the control animals The animals were then sacrificed and histologic examination showed that in the scorbutic guinea pigs the epidermis of the laparotomy wounds appeared normal, but that the underlying connective tissues were abnormal The degenerative changes consisted of fibroblastic proliferation, regression of connective tissue elements, and hemorrhage It was concluded that these studies and other evidence indicated that adequate ascorbic acid intake is essential not only for normal healing in the period immediately following trauma but also for the maintenance of previously formed scar tissue Scar tissue is apparently more susceptible at least in animals, to vitamin C deficiency than is normal tissue There is other evidence that in vitamin C deficiency the fibroblasts mature but are unable to produce the extracellular components of connective tissue, i e, ground substance and collagen.

POTASSIUM AND WOUND HEALING We were not able to demonstrate a deleterious effect of a dietary potassium depletion on the healing of skin, fascia, or stomach in dogs.[11]

BODY FLUID METABOLISM ACUTE ANEMIA, LOCAL TEMPERATURE AGE, EMOTION AND HORMONES These factors do not materially influence wound healing in ordinary surgical practice. The potential adverse effect of steroid therapy on wound healing has not materialized.

Clinical Wound Management

EFFECT OF EARLY AMBULATION ON WOUND HEALING In 1941 Leithauser and Bergo[19] in the United States again focused attention upon the advantages of early postoperative ambulation but many surgeons remained apprehensive that the incidence of wound dehiscence would increase In allaying this concern a valuable experimental study was that of Royster McCain and Sloan[29] who showed in dogs that (1) the general condition of the ambulated animals was improved over that of the controls, (2) a significant number of animals in the ambulated group gained weight while the controls generally lost weight, and (3) the tensile strength of the postoperative abdominal wound in the ambulated group did not differ significantly from the values in the control group These authors noted that their curves for wound healing of the skin, anterior rectus fascia, and peritoneum posterior rectus fascia did not vary materially from those published in 1929 by Howes, Sooy, and Harvey[16] (Figs 36 and 37)

EFFECT OF PREGNANCY ON TENSILE STRENGTH OF HEALING LAPAROTOMY WOUNDS IN RATS Localio and Chassin[20] reported that pregnant rats showed a marked diminution in the tensile strength of healing laparotomy wounds as compared with normal, nonpregnant female rats Since in our own experience wounds made in pregnant women have healed satisfactorily, it would appear advisable to await further study before reaching a negative decision regarding the healing capacities of tissues in such patients

THE EFFECT OF ROENTGEN RAYS ON WOUND HEALING It has been a common belief that wound healing is poor following irradiation, and many surgeons have hesitated to operate through skin which had been heavily irradiated Nevertheless Lawrence, Nickson, and Warshaw[18] obtained experimental evidence that irradiation does not seriously impair wound healing. They studied the effect of irradiation on the healing of standard abdominal incisions in young rats over intervals of from one to three months following the exposure. The irradiation administered in the preoperative period was in the clinical therapeutic range, and the wounds were comparable to clinical laparotomy incisions Studies of the rate of healing of these wounds in terms of tensile strength were carried out and showed that all wounds reached the maximal strength range, although there was some delay in the rate of attainment of this strength by the irradiated wounds Delay in healing was most marked in the wounds

receiving irradiation immediately or within one week before surgery The difference in the healing curves of tissues irradiated three weeks, five weeks, eight weeks, and twelve weeks prior to surgery was not great It was noted by these authors that the healing of surgical wounds in recently irradiated tissue is impaired, in a practical sense, only in terms of rate of healing and not in terms of the final wound strength They felt that the data also appeared to demonstrate little or no practical advantage in delaying surgery more than three weeks after irradiation The presence or absence of irradiation-induced skin erythema, *per se*, seemed to have little effect on the rate of wound healing in the rat

In passing, the clinical hazard of excessive x-ray dosage should be emphasized Few surface lesions are more distressing than a severe radiation "burn"

The Infected Wound

Wound infections have not been abolished by antibiotic therapy In fact, it often seems that these complications are now as common as ever Therefore, it is important to diagnose purulent collections promptly, when prophylactic measures have failed and an infection has developed

There are, of course, all types and degrees of infection, not only with regard to the actual tissues involved but also to the particular bacterial organisms encountered For our purposes here, however, let it be assumed that the infection is due to a staphylococcus What findings may be anticipated?

General or *systemic signs* may appear before *local evidence* is present Fever, tachycardia, and malaise may suggest that one of the common postoperative febrile complications—pulmonary atelectasis, wound infection, phlebitis, or urinary tract infection—is present or impending A wound infection does not usually become apparent until several days following the operation, but sooner or later the wound becomes tender, painful, indurated, erythematous, or swollen—or all of these Yet, actual suppuration may not have occurred, and one is ill advised to probe around in t
until the site of the probable
manifests itself—which it almos
will do, if hot wet soaks are comb
watchful waiting Once the absc
cated, it is readily evacuated by op
recent incision with a hemostat a
ing a drain Toxic systemic mani
usually cease promptly when pur
lections are afforded free drainag
outside

Wound Disruption: Causes, Pre and Management

CAUSES *Suture material* The c
wound disruption in surgical patie
in part, been alluded to previously
ture material has not been mentione
ever substance is used, it is impo
to strangulate the tissue of the
wound margins by improper suture
While the type of suture material us
a factor of the greatest importance,
portant that the strength of the su
terial be at least adequate For exa
have had the experience of having a
lar patient retch as he was emerg
anesthesia, with a resulting audi
of the silk sutures with which th
had been repaired, recurrence of th
occurred then and there Since e
coughing or straining during the f
days postoperatively cannot always
ished, the repair must be firm On t
hand, the suture material should no
cessively large for the purpose E
results are obtained by excellent s
whether silk, chromic catgut, stainl
wire, or cotton is used for fascial r

Metabolic disorders It has appea
that patients with diabetes mellitus a
prone to wound disruption than are p
without this metabolic disorder Th
be true of patients with Cushing's syn

Protein deficiency The direct cor
between inadequate protein stor
wound healing has been mentioned P
with advanced malignancy, who usua

protein deficient, are apt to exhibit poor wound healing In such individuals every possible precaution against wound complications is in order

Type of incision It is often claimed that the vertical incision is less likely to result in wound separation than is the transverse incision or *vice versa* However, in a study of the factors involving wound dehiscence in 1000 cases Marsh and his associates [4] found no difference in the incidence of wound disruption with vertical as compared to transverse incisions They concluded that the important factors predisposing to wound dehiscence were (1) *Nutritional deficiencies* incident to carcinoma, infection, or other debilitating factors (2) *Mechanical factors* such as violent coughing or abdominal distention. (3) *Type of wound closure* (In a controlled series of 500 consecutive cases in which through and through retention sutures plus layer closure were used systematically there was no incidence of wound dehiscence in uncomplicated transverse or vertical incisions This was not the case in a series of 500 cases in which systematized wound closure was not used, even though all other factors were comparable) (4) *Age* (The average age of patients with wound separation was 56 years as compared to an average age of less than 49 years for the 966 patients whose wounds healed primarily).

Type of closure Certain considerations have been mentioned above Hoerr, Allen, and Allen[14] compared a mass closure with wire and layer closure with silk At the beginning they acknowledged that (1) accurate approximation of the wound edges is essential (2) suture material should be as fine as is consistent with safety (3) suture material should be kept at a minimum and (4) nonabsorbable suture material produces little inflammatory and foreign body reaction in the wound but may act as an unpleasant nidus of infection at a later date, particularly in a potentially infected wound Such wounds may "spit" silk even in the absence of frank sepsis. These authors studied a series of 127 abdominal incisions in 122 patients, they alternated between a method employing No 31 stainless steel wire as an interrupted suture through peritoneum, muscle, and the rectus fascia, as compared to a layer to-layer technic with interrupted 00 silk sutures The skin was closed with metal clips in the wire wounds and with interrupted silk in the silk wounds The group of 66 wire closures and the group of 61 silk closures were roughly equivalent from the standpoint of location of incision, length of incision duration of operative procedures, and potential contamination at the time of operation There was approximately the same incidence of early postoperative complications in the two types of wounds, and there was no detectable difference in the appearance of the wounds Postoperative pain was the same In the available follow-up, late complications appeared to be about the same with the exception of minor infections for sinuses which occurred more frequently after a closure with interrupted silk. There had been three hernias in silk wounds to one in a wire wound Wire closures were simpler to execute, required only three-fourths as much time as silk closures, and seemed to be especially well adapted for use in patients with long incisions

We prefer the above type of wire closure—with or without heavy silk retention sutures—in any wound where there exists a strong possibility of postoperative dehiscence This applies particularly to patients with advanced malignancy, potentially infected wounds and obese subjects There are few problems due to wire *per se* if each wire is cut separately just at the knot to avoid subsequent impingement of the wire against the undersurface of the skin, should the patient lose weight In younger persons who present no particular reason to suspect that wound difficulties may arise, chromic catgut is commonly used for peritoneum posterior rectus sheath closure and interrupted silk is used to close the anterior sheath and the skin in our clinic But, again, whatever the suture material employed there is no substitute for careful placement of the sutures so as correctly to approximate the layers of the abdominal wall

Increased intra-abdominal pressure We are convinced that increased intra-abdominal pressure—whether due to coughing, hiccups, vomiting, intestinal distention, or ascites—is a major cause of the wound disruption in many instances

TREATMENT OF WOUND SEPARATION One should be keenly alert to the possibility of wound separation following aortic resection, or, as noted, in the patient who is distended, who has infection in the wound, or who is coughing, straining or vomiting An additional factor which frequently suggests impending wound separation is the drainage from the wound of a profuse amount of serous or serosanguinous material Since such material often represents fluid from within the peritoneal cavity, this calls for immediate precautionary measures The first thing to be done is to apply wide adhesive tape, beginning far around on one flank, crossing over the incision, and being secured on the other flank—placed in such a way as to put traction on the skin lateral to the wound edges in order to diminish tension on the suture line itself In this way healing of the skin may often be secured even though separation of the peritoneum and fascia has occurred beneath This of course limits wound separation to the formation of a hernia, thus avoiding the far more serious complication of actual evisceration If evisceration is minimal, such as the appearance of a single loop of bowel through the skin edges, this may be replaced, the wound taped as described above, and the patient not taken to the operating room —if the patient's condition is considered sufficiently critical to warrant this choice of conservatism

To place wire sutures in a wound that has separated is usually a difficult matter unless enough anesthesia can be given the patient to secure relaxation of the abdominal wall For this reason, and since wound evisceration most commonly occurs in individuals who were poor operative risks initially, it may be desirable to avoid anesthetizing these patients, if by means of adhesive strapping this necessity can achieved The reason adequate anesthesi required is that the edges of the heal (and often infected) wound are friable will not hold the sutures if the patient straining the while With taping, if onl hernia results it can be repaired later an elective procedure in a good risk patie

If frank evisceration has already curred, it is usually mandatory to take patient to the operating room, use what esthesia is essential, replace the loops bowel, and close the wound with throu and-through stainless steel wire sutu These include all layers of the abdomen a are twisted sufficiently tightly to coapt edges of the abdominal wall Additional sl sutures may be placed between the hea wire sutures As these heavy sutures drawn up tight, the examining finger mu make certain that no loop of bowel caught or can later herniate through one the wire loops Though these sutures a left in place from 14 to 21 days, it may necessary to loosen them from time to tir as the wound swells with edema

Transplantation of Tissues

Historical Review

PARABIOSIS Among the early attempts the transplantation of one tissue to anoth tissue were those which were concerned wi parabiosis in mammals, the actual joini of one animal to another (Fig 40) Th earliest work in this field was done by Pa Bert, performed in the 1860's in Claude Be nard's laboratory in Paris, and his first suc cessful pairing of two young albino rats wa achieved on April 7, 1862 In this pione experiment, it was demonstrated that in jected fluid passed from the external jugu lar vein of one rat, through cutaneous vess anastomoses, to the femoral vein of the part ner Further details of his general work i this field were published later, when he re viewed the regenerative capacities of lowe animals, contrasted them with those of bird and mammals and discussed the grafting o

skin, tails, and feet. Apparently the parabiosis technic was the result of attempts to accomplish successful grafts from one animal to another In white rats the tails were transplanted to other rats of the same age but it was not possible to produce positive results between different species, such as between the rat and guinea pig, cat rat, or mammals birds Various means of parabiosis were employed some of the parabionts being attached only by suture of the skin of adjacent flanks while with others fusion of the muscular body walls as well was performed In many autopsies Bert demonstrated generally by injection technics that vascular connections of capillary size were formed. Another method of showing cross circulation was that of injecting belladonna into one partner and noting dilatation of the pupils of the attached animal within 20 to 30 minutes Successful skin homografts were made by separating the parabionts after two months of parabiosis leaving part of the skin of one rat attached to its partner The flap persisted in its new site.[7]

Following the work of Bert, the technic of parabiosis was little used until it was revived in Germany by Sauerbruch and Heyde[40] in 1908 In 1909 Rous[34] published a paper in the United States in which he showed that parabiosis of a rat resistant to tumor transplantation did not affect the tumor susceptibility of its partner Since then parabiosis has been used as an experimental tool in many fields including studies of skin grafting, kidney removal, irradiation effects, nutritional deficiencies, pituitary gonad relationships diabetes mellitus, and the metabolic effects of malignant tumors

TISSUE CULTURE. In 1878 Claude Bernard[1] emphasized the paramount importance of the internal chemical environment of living tissue It was appreciated that this internal environment is not only the product of tissue metabolism, but that it in turn reacts upon the tissues thereby further regulating tissue activity The development of tissue culture methods was a natural outgrowth of such ideas for to study the functional prop-



Fig 40 Parabiotic mice Parabiosis is here achieved by joining the parabionts along the flanks (see text)

erties of cells and how they influence, or are influenced by, their immediate environment, it was necessary to isolate these cells in a way which would eliminate the continuing effect of the parent organism

The first experiment in tissue culture was carried out by Wilhelm Roux[38] in 1885, when he announced an 'explanation' of living tissues The medullary plate of a chick embryo was isolated and was placed in a warm saline solution, and eventually Roux was able to demonstrate that the closure of the medullary tube was a function of the constituent cells rather than a result of mechanical pressure of surrounding tissues Subsequently other investigators were able to maintain living tissues in salt solutions or in body fluids but the first actual visualization of cell growth is credited to R G Harrison,[1-] who in 1907 observed the migration of nerve fibers in a frog embryo under the microscope He also described an important basic principle of tissue culture technic, namely that the *cells will not grow when floating freely in the nutrient fluid but must be attached to a solid substrate, such as clotted lymph* Later other workers observed cells undergoing mitosis *in vitro*

Yet important as these pioneer studies were the technic of tissue culture was established on its modern basis by Alexis Carrel He developed most of the presently used technics of tissue culture and demonstrated that adult mammalian tissues could be grown successfully in blood plasma In 1913 Carrel[4] reported that the addition of

aqueous extracts of embryos made possible continuous cell proliferation, and he maintained a strain of chick fibroblasts in culture for over 30 years Moreover, his laboratory at the Rockefeller Institute became perhaps the world center for tissue culture work, and the technics employed there have been recorded in book form by Parker[30] In 1911 Rous[37] demonstrated that a virus from a chicken cancer would produce a tumor when injected into a healthy fowl, and that the virus could be recovered again by filtration Some years later a cancer was produced by exposing normal tissue *in vitro* to the filtered extract of Rous' sarcoma and also by application of carcinogenic agents to the normal cells in tissue culture

The most commonly employed methods of tissue culture are the hanging drop method, the roller tube technic, and the flask method In the first, a fragment of tissue is placed in a drop of culture medium on a clean cover slip, which is then inverted over a hollow-ground microscope slide and sealed with paraffin before being placed in the incubator. In the second method, small test tubes are used and fragments of tissue are planted in a thin plasma coagulum on the side of the tube and then the tube is sealed and placed in the incubator where it is slowly rotated This rotation facilitates the interchange of oxygen, food materials, and metabolites between the cells and the medium In the flask method, Carrel flasks or other specially designed glass flasks are used

Modern Ideas and Experimentation in Homotransplantation

The basic problems in tissue homotransplantation have nowhere been more lucidly presented than by Leo Loeb[21] in his classic work entitled *The Biological Basis of Individuality,* which incorporated most of the important research prior to 1945 He stated that "there is inherent in every higher individual organism, something which differentiates him from every other individual which can be discovered by observing the reactions of certain cells and tissues belon ing to one individual toward the tissues a cells of another individual of the same sp cies It is not only the cells and tissues one individual, however, which react t wards these elements of another individu in such a specific manner, but there is al a substance in the body fluids of one in vidual which responds towards all cells a tissues of another individual in accordan with the degree of genetic difference b tween these two animals"

The genetic factor that precludes a pe manent transplantation of blood-nourish tissues from one animal to another of t same species for any length of time excep in closely inbred animals of lesser degree genetic dedifferentiation has been empha sized In man, the only homotransplan that have been definitely proved to take su cessfully have been transplants betwee identical twins, or to individuals with agam maglobulinemia The absence of immun gamma globulin was described by Bruto in 1952 Subsequently Good and Varco[8] per formed successful skin homografting o such a child These workers reviewed th evidence in favor of the hypothesis tha the failure of homotransplantation has a immunologic basis as follows (1) the tim required for rejection of homografts is i the same time range as that required fo antibody production, (2) the speed of re jection of homografts is related to the dos of "antigen" supplied, (3) the circulation o blood or lymph without barrier to antibody is essential for the rejection of homotrans plants, (4) evidence for secondary response or so-called anamnestic reaction is found in the more rapid rejection of a second antigenically similar homograft than of the first, (5) agents such as total body irradiation and cortisone that suppress antibody formation may prolong the survival of homotransplants, (6) desensitization with skin antigens results in prolonged survival of homologous skin grafts, and (7) rejection of homotransplants of skin is associated with the appearance of antibodies against

donor cells and tissues in the circulation of the host

Behavior of Autogenous Human Tissue Grafts

The transfer of autogenous tissues has long been successful and is commonly accepted as a routine practice, particularly with respect to skin, nerve, bone tendon, and certain other tissues Peer and Walker[31] studied free autogenous human grafts under two conditions of transfer first, in contact with unlike tissues and second, in contact with like tissues The cells of cartilage, septal bone, fascia tendon, and surface skin grafts all tended to survive, the tissues retaining their specific structure Thus, cartilage appeared as cartilage, septal bone as bone fascia as fascia, and so forth, regardless of whether the recipient site consisted of like or unlike tissue. (This is not true of blood vessel grafts, as will be seen later) Rib, tibial and iliac bone grafts *in contact with unlike tissues* were replaced by host fibrous tissue, regardless of the thickness or the thinness of the grafts or the vascularity of the host site The bone cells in the grafts often survived transplantation, but they were unable to maintain their calcified intercellular material which was absorbed and replaced by host fibrous tissue in a period of about eight months Rib tibial, and iliac bone grafts *in contact with bone* tended to retain their calcified structure About 50 per cent of the fat cells in fat grafts survived transplantation and these surviving fat cells, together with their connective tissue framework, comprised the bulk of the fat graft that remained one year or more following transplantation. There was no evidence that cellular elements from the host tissues took on fat and replaced fat cells in the graft Fat grafts transplanted in contact with fat had the same fate as fat grafts transplanted in contact with unlike tissue

Muscle cells or fibers in free muscle grafts always degenerated and disappeared following free transplantation irrespective of whether the graft was in contact with unlike tissues or with muscle The fibroblasts in the connective tissue framework of muscle grafts survived transplantation, and these cells together with infiltrating host fibroblasts converted the muscle grafts into a small fibrous tissue band in a period of about one month

The epidermis, hair follicles, and glands tended to degenerate and to disappear in dermal skin grafts This doubtless accounts for the relative infrequency of inclusion cysts when buried dermal grafts are used for the repair of inguinal hernias The fibroblast cells in the dermis survived transplantation, associated with the bundles of collagenous and elastic fibers which constituted the bulky intercellular portion of the dermis.

When nerve grafts were transplanted in contact with unlike tissues, the fibroblast cells in the framework of the graft survived and proliferated to such an extent that they completely replaced the degenerating axons and myelin sheaths The Schwann cells survived the initial shock of transplantation but disappeared among the larger number of proliferating fibroblasts When nerve grafts were transplanted in accurate contact with nerve, the Schwann cells survived but the axons and myelin sheaths degenerated and disappeared A few axons from the proximal host nerve grew down through the unobstructed channels in the nerve graft and continued on into the distal end of the host nerve.

It was concluded by these workers that the vascular system in free grafts tends to survive transplantation, and that early circulating blood for these surviving blood vessels of the graft is provided through direct anastomosis of host and graft blood vessels If this circulating blood reaches the centrally located cells in four days, the cells may not die from the effects of their accumulative waste products and lack of oxygen.

Homografts

ATTEMPTS TO MODIFY FATE OF HOMOGRAFT There have been numerous attempts by var-

ious workers to modify, on the one hand, the host reaction to the homograft and, on the other, to influence the graft so that it would not act as an antigen The protein of grafts has been denatured by heating, irradiation, and other treatment, the hosts have been given antihistaminic agents, adrenocorticotropic hormone (ACTH), cortisone and other substances which were considered likely to minimize the antibody reaction of the host to the graft Generally speaking, all such efforts have been unsuccessful, for as yet no truly satisfactory method of homografting has been achieved, certainly in the sense that the transplanted tissue maintains its individuality and actually functions It will be seen that arterial homografts are useful even though the donor cells are eventually replaced by host tissues

In studies of skin homografting in chicks, Cannon and his associates[3] concluded that, taken all together, their observations indicated that tissue specificity in the chick is gradually assumed, probably beginning some time in the latter part of incubation It is not completed in the individual as a reacting organism until the seventh day following hatching The tissue specificity of the skin is not invariably detectable by 1-day-old chicks until the donor chick is 14 days of age

CLINICAL USES OF HOMOGRAFTS *Skin grafts* Skin *autografts* are used commonly, wherever coverage is required, but the most frequent use of skin *homografts* is in the grafting of burns where the status of the individual or the extent of the burn precludes the immediate availability of sufficient amounts of the patient's own skin (autografts) to cover the burn wounds While in certain clinics the use of such homografts is strongly advocated, it has never solved the problem of successfully covering the patient's wounds permanently, for these homografts usually survive for only several weeks and then gradually disappear Therefore, regardless of the number of homograft "takes," it will eventually be necessary to graft the patient with his own skin Even so, the successful homograft constitutes a physiologic dressing, though temporary, and may be lifesaving

The chief factors which limit the use of homografts are (1) the uncertainty of even a temporary "take" of the graft when the general condition of the recipient is such as to contraindicate autografting, (2) the difficulties of obtaining skin donors, (3) the inconvenience to the skin donor if sizable grafts are taken, (4) the dangers of a generalized allergic reaction to foreign skin, (5) the uncertainty of the survival time of the graft if a primary "take" occurs and, (6) the undesirable local effects as the homograft begins to "melt away" before the patient is ready for autografting[22]

To overcome some of these objections, however, many have advocated the use of homografts obtained at autopsy and preserved The upper limit of time which such homografts may be stored has not been fully determined, but it is certainly a matter of weeks if not months

Factors in the host which influence success in skin grafting —Whether the graft is to be autogenous or homologous, certain nonantigenic factors materially influence whether or not the graft will "take" First, an infected recipient area is notoriously unfit for grafting Second, the presence of dead tissue is an additional contraindication to grafting, and a healthy granulating fresh surface is to be strived for Third, among other factors the general condition of the patient is important, malnutrition and anemia are factors which, for reasons as yet poorly defined, diminish the number of takes

Split thickness skin grafts, especially autografts, will take in a variety of places such as the exenterated orbit, the stomach from which the mucosa has been stripped, the mouth, in hernia repairs (*buried*), and elsewhere

Blood vessel grafts Although sporadic vessel transplantation had been performed much earlier, it was Carrel,[5] in 1907, who established that blood vessels could readily

be preserved and transplanted in experimental animals[8] Yet, despite these early studies which clearly presaged the clinical use of blood vessel grafts, application of this early work did not gain momentum and a number of decades passed before the subject was re-examined in the experimental laboratory and applied in the clinic In 1949 Gross[9] and Peirce[32] and their associates published their clinical experience with arterial homografts, and securely established the technic in modern surgical practice

Autogenous vessel grafts —Because of the basic failure of most efforts at homotransplantation of tissues naturally the first choice for replacement of vascular defects was that of using vascular grafts from the same individual to bridge arterial defects Autogenous grafts would have two advantages (1) fresh tissue would be available and (2) the autogenous tissue would remain a living structure after transplantation. Unfortunately, few arteries can be spared and so venous autografts were used fairly widely for a time However, studies soon showed that there was a marked tendency for unsupported fresh venous autografts to dilate in the thoracic aorta of both the growing pig and the adult dog[17] Therefore the use of venous grafts has been largely abandoned

Homologous vessel grafts —Following the original reports by Gross and his associates regarding the temporary storage by refrigeration of arterial homografts and the successful clinical use of such material a prodigious volume of work was done regarding methods by which the grafts might be stored over extended periods of time At first it was thought necessary to maintain the grafts in a viable state, but it gradually became apparent that such was not necessary since the homograft actually functioned only as a bridge and was eventually replaced with the host s own tissue, *with the possible exception of the elastic fibers* The most common method of storing or preserving arterial homografts is that of freeze-drying or lyophilization, but an even simpler method, which appears definitely promising is that of merely placing the fresh graft in 70 per cent alcohol until it is to be used

Results with arterial homografts —The initial results with homografts have been gratifying Gross and his associates have now had arterial homografts in place, following resection of coarctations of the aorta, for approximately eight years without evidence of significant deterioration of the graft However, there is no question but that grafts inserted in the abdominal aorta in older individuals not infrequently become aneurysmal or become thrombosed

Heterogenous vascular grafts —These have not been successful

The use of plastic materials for bridging arterial defects —Since the advent of homografting the volume of vascular cases which may be aided by such arterial replacement has increased to the extent that it is not always possible to have available a suitable homograft For this reason—in addition to the fact that homografts themselves are not perfect arterial substitutes—there has been much interest in the use of various plastic materials for arterial replacement. In 1952 Voorhees, Jaretzki, and Blakemore[43] reported the use of a porous plastic (Vinyon N) cloth tube, and since that time various other substances have been employed such as nylon, Ivalon, Orlon, and others These materials are now regularly employed clinically They are subject to most of the same complications as are homografts and they probably will be attended with approximately the same degree of success—which is not inconsiderable when the usual outlook for the unoperated patient with an aneurysm is contemplated.

Growth of anastomoses —One technical point of probable importance is that in inserting a graft in younger individuals (and in suturing arteries at any time in the younger individual) it would appear advisable to use interrupted sutures for at least a portion of the vascular anastomosis to allow for growth of the vessel as the individual enlarges While the everting mat

tress suture, either interrupted or continuous, is the time-honored method of suturing blood vessels, a simple continuous over-and-over suture around the entire circumference of the vessel is quite satisfactory, certainly in adults

Bone grafts Autogenous —The use of autogenous bone grafts is well established and such grafts are, in general, readily incorporated into the bony structure at the new site The most common source of such bone is the crest of the ileum, the tibia, or rib These grafts are often used in the form of chips rather than long solid segments of bone

Homologous —The great interest in the use of homografts of all types has, of course, included bone Homologous bone, particularly as ground bone, has been used widely, but it is not as readily incorporated into the tissues of the host as is autogenous bone

Cartilaginous grafts Autogenous —Autogenous cartilaginous grafts have been used with reasonable success for many years

Homologous —In reviewing the present status of cartilaginous grafts, Schofield[41] offered the following conclusions (1) there seems to be no doubt that cartilaginous implants can provide a satisfactory filling material in contour defects for at least two years in over 70 per cent of the clinical cases, (2) results suggest that 50 per cent of the implants may show evidence of absorption by the end of two years

Homotransplantation of the lung Homotransplantation has been attempted by a number of workers It has been demonstrated that the homologous transplants may be placed in an animal and then the animal's other lung immediately resected, leaving only the grafted lung for oxygenation of the blood Hardin and Kittle[10] had two animals which survived for six and nine days, proving unequivocally the functional ability of the homologous lung during these periods However, although the operative technic of transplantation of one entire lung has been demonstrated to be feasible, as with other types of homotransplantation the lim itations imposed by foreign protein im plantation appear responsible for the pre ent failure of these organs to survive[20] I contrast, autogenous lungs reimplanted in the same animal do survive

Homologous transplantation of the hear Homologous heart transplantation w achieved by Neptune and his associates They reported three instances in which th heart and lungs had been successfully trans planted in dogs under hypothermia, with th donor heart maintaining all circulation an allowing return of reflexes, spontaneous res piration, restoration of normal body tem perature, and survival of the animal up t six hours following surgery Neptune and hi associates pointed out that, while Mann an co-workers[23] had previously transplante intact mammalian hearts from one anima to another in various parts of the vascula system, the donor heart had not been previ ously called upon to perform the functio of maintaining complete circulation in th recipient animal

Renal homotransplantation A prelimi nary study of renal homotransplants in dog was reported by Murray and his associates in 1953 It was concluded that host rejection of kidney homotransplants is not accompanied by the suppression of serum complement that has been observed in some types of acute renal failure However, although some homografted kidneys did establish a variable urine flow for some 12 to 96 hours, ureteral necrosis and other evidences of transplant failure then became apparent More recently, several teams have reported transplantation of kidneys, both experimentally and in human cases Even so, successful and permanently functioning renal homotransplantation has been accomplished only between identical twins

Other homotransplantation studies Almost all of the readily approachable organs have been transplanted at one time or another, particular attention being accorded endocrine organs By and large, homotrans-

plantation has not thus far been successful The sporadic reports of successful homografts in which the original transplant achieves a new blood supply and continues to grow have rarely been substantiated by subsequent experimentation

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Chapter 5

Surgical Microbiology

Far from having been abolished by antibiotics surgical infections continue to represent major sources of morbidity and mortality To be sure many of the most feared infections, such as staphylococcal and streptococcal septicemia, were brought under control during the 1940's, and most streptococcal infections still respond promptly to properly selected antimicrobial agents In the case of staphylococci however the incidence of resistant strains has increased rapidly now almost 80 per cent of those isolated from hospital wound infections fail to respond to penicillin. Accordingly staphylococcal septicemia is again a common and often a lethal surgical complication. Thus, while the epidemiology of bacterial infections has changed over the past 20 years the problems before the microbiologist were never more challenging than now

The primary purpose of this chapter is then to outline certain of the physiologic relationships which exist between microorganisms and the host. A second objective is to survey certain of the therapeutic requirements encountered in the management of surgical infections.

Relationships between Microorganisms and Host

In the preparation of the discussion which follows liberal use was made of the penetrating monograph by Dubos[8] entitled *Biochemical Determinants of Microbial Diseases* The following questions will be considered in this discussion (1) when does bacterial infection become bacterial disease? (2) normal mechanisms for clearing bacteria from the tissues, (3) a consideration of bacterial invasion—criteria of pathogenicity, (4) the increased susceptibility of the diabetic patient to infection, (5) immunity and inflammation and (6) systemic effects of infection

When Does Bacterial Infection Become Bacterial Disease?

There is now abundant evidence that many of the organisms which cause the usual surgical infections are commonly harbored by normal subjects For example, streptococci staphylococci, colon bacilli, anaerobic organisms, tubercle bacilli and certain viruses such as that of herpes simplex are normally found within or upon the human body Therefore, unlike the situation which existed during the nineteenth century when great epidemics of pestilence swept whole countries with a heavy mortality, the present day organisms that are the source of much morbidity and of significant mortality are microorganisms that are "endemic" in most healthy individuals In other words, the physician in the present part of the twentieth century is not primarily concerned with cholera or yellow fever or even typhoid fever or smallpox he is concerned with staphylococcal and streptococcal infections and to a declining extent tuberculosis Viruses are prominent. So while the problems which confront the microbiologist are less spectacular than previously, they are not greatly reduced in over all dimensions.

It has been suggested that, now that the goal of modifying or limiting epidemics has been reached it is time to acknowledge that

mortality rates no longer constitute satisfactory yardsticks with which to measure the importance of medical problems [9] If one were to use as a criterion the amount of life spoiled by disease, instead of measuring only that destroyed by death, or the number of days lost from pleasure and work because of so-called minor ailments, or merely the sums paid for drugs, hospitals, and doctors' bills—then the toll exacted by microbial pathogens would still loom large indeed "Microbial diseases have not been conquered Rather, scientists have resigned themselves to the belief that a relative protection against them can be had only at the cost of a huge ransom "

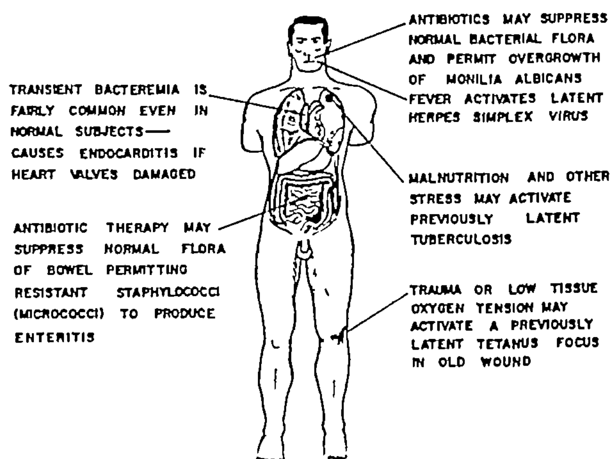


Fig 41 There is a vast difference between the mere presence of microorganisms in the body, on the one hand, and overt disease due to these microorganisms, on the other



Fig 42 Multiple and extensive suppurative foci of the buttocks For many years this patient had drained much pus each day from multiple fistulous or sinus tracts While the mortality under such circumstances is not great, the morbidity due to such chronic infections is enormous

In considering further the types of infections which should be of the greatest interest to the modern scientists and microbiologists, Dubos points out that the major effort should no longer be directed toward the study of diseases which produce a highly lethal exotoxin, such as diphtheria and tetanus attention should be focused on the common microorganisms which do not manifest themselves by any dramatic effect but cause slow, low grade intoxications These low grade toxins interfere with the optimum performance of everyday life, and may cause an enormous amount of inefficiency (Fig 42)

BLOOD STREAM INVASION Certain types of microorganisms are constantly present in the intestinal tract and in other parts of the normal body, and it has long been realized that from time to time some of these organisms do invade the blood stream, for even apparently healthy human beings and animals may occasionally exhibit a positive blood culture Even so, while such brief bacteremias may cause no obvious symptomatology, in reality they probably do have an adverse effect upon health It will be seen later in this discussion that relatively small amounts of the cellular constituents of gram-negative bacilli can be responsible for a large variety of disease manifestations, ranging from a febrile response to profound disturbances in sugar metabolism We have cited the case of a patient (p 18) who developed diabetes mellitus, requiring almost 100 units of insulin per day in addition to a strict diet, all this while he was being treated intermittently for an infected lung cyst After the cyst had been surgically excised to simplify management of the diabetes, the absence of chronic infection was followed by a regression of the diabetes until no insulin was required and the diet was a matter of no particular annoyance

STIMULI WHICH MAY PRODUCE OVERT DISEASE ...ATENT INFECTION (Fig 41) First, the ...erpes simplex is probably acquired

by the individual early in life and requires only the presence of fever, however induced, to become active and produce the common fever blister of the lip Second, starvation and other privations of prisoners of war commonly resulted in a marked increase in tuberculosis among these individuals who unquestionably had, for the most part, carried tuberculosis organisms most of their lives As soon as these individuals were released from prison and given better environmental conditions and adequate food, but given no specific drug therapy the tuberculosis usually improved rapidly As an example of a highly specific nutritional relationship, a diet deficient in pantothenic acid permits the overt manifestation of previously latent corynebacterium infection in albino rats Third, whole body irradiation of sufficient degree results in an impairment of the antibacterial defenses of the body and produces a bacteremia and toxemia which may result in death This emphasizes the fact that while the barrier constituted by the epithelium of the skin or intestine is an important one it does not constitute the only protection against invasion by mircoorganisms for this barrier is intact following whole body irradiation In the tissues and other body fluids there are multiple antimicrobial agents as will be described which are probably more important in defending the body against bacteria than is the skin or the intestinal mucosa Fourth, there is a greater incidence of fungous infections of the mouth in patients receiving antibiotic therapy than is normally the case It appears that the new microbial population which follows in the wake of the microbial flora which was present prior to the administration of the antibiotic permits the fungi notably *Candida albicans* to multiply rapidly the fungus is then able to cause disease where normally, even though it is probably present in the mouth, it does not do so

An additional example of the fact that the administration of antibiotics may so alter the normal flora as to allow the overgrowth of one organism is the now generally recognized staphylococcal enterocolitis (p 144)

BACTERIOPHAGE. A circumstance which militates against bacterial growth is illus trated by the relationship that exists be tween the bacterium and the bacteriophag which the organism itself may carry I nature, many bacterial species, termed "ly sogenic," carry an inactive form of one c several bacteriophages potentially capabl of causing lysis of the bacterium itself Th inactive form of the bacteriophage (prc phage) is apparently reproduced with eac bacterial division without causing any de tectable disturbance in the bacterial cel However, if the bacterial cell be irradiatec it will frequently be lysed. This may be du to the fact that the prophage renders th bacterium more sensitive to the radiatioi or that the radiation renders the bacteriur susceptible to the prophage or that bot circumstances are required for the lytic phe nomenon To complicate the matter sti further it has been shown that in som cases the activating effect of radiation ca take place only in media of certain com position, thus rendering the problem of th etiologic determination of the disease lysi still further obscure[29]

Phage activity may of course alter th capacity of the bacterium to produce dis ease and phages are employed for typin organisms such as staphylococci.

Normal Mechanisms for Clearing Bac teria from the Tissues

The intestinal tract, the skin, and th respiratory tract normally contain larg numbers of a variety of bacterial forms From time to time some of these bacteri penetrate into the blood stream causing a transient bacteremia, but they do not caus overt infection. On the other hand, if an or gan becomes damaged, as with rheumati damage to the valves of the heart, thes agents (which are normally present an which are considered to enter the bloo stream innocuously at other times) may cause a disease such as subacute bacteria endocarditis

Rates at which bacteria can be removed from the blood stream were studied by Price and his associates [34] They found that if organisms were infused at a rate of less than 1000 organisms per minute, no bacteremia could be demonstrated by blood culture, if the number of organisms introduced significantly exceeded 1000 per minute, positive blood cultures could be obtained in the dog

Thus, as with experimental tumor "takes," the probability of bacterial infection increases with the size of the dosage In either case the body defenses may be overwhelmed

The organs which filter the bacteria out of the blood stream are the reticuloendothelial elements in such organs as the spleen, liver, bone marrow, and lung

A Consideration of Bacterial Invasion: Criteria of Pathogenicity

The most important difference between a pathogenic organism and a nonpathogenic organism consists, largely, in the ability of the former to multiply within the tissues of the host and to maintain a satisfactory rate of multiplication In other words, the fundamental point of difference is not necessarily that the pathogenic bacterium elaborates a more toxic factor than does the nonpathogenic organism, it is that in a particular setting the one can grow and the other cannot [9]

INTRACELLULAR PROCESSES It has been noted that most pathogens as well as saprophytes are rapidly engulfed by various types of phagocytic cells, some immediately becoming surrounded by a vacuole and others appearing to remain free within the cytoplasm The chemical changes which occur in the cell as it engulfs the foreign material are largely unknown, but it has been shown that following the engulfment of certain types of foreign particles and bacteria the intracellular pH falls to a very low level, at least in the phagocytic vacuole In addition, there are studies which suggest that cellular metabolism is modified in such diseases as diabetes, and thus that it can be altered by hormones (see below) Yet, to acquire detailed knowledge of intracellular infecti[ons] which as Dubos points out represent [the] largest number and the most importan[t of] the infectious diseases, a type of chem[ical] analysis is required for which methods [have] not yet been developed.

ATTENUATED MICROORGANISMS NATURE [OF] REDUCED PATHOGENICITY It is of import[ance] to realize that the so-called "attenuated [or] "avirulent" organisms which are often [used] to produce active immunity against a v[iru]lent infection are attenuated or aviru[lent] only in the sense that their prolifera[tion] *in vivo* is not sufficiently extensive or [pro]longed to lead to serious disease In [this] sense, let us compare bovine and hu[man] types of virulent tubercle bacilli Injec[tion] of a very few bacilli of either type [in] guinea pigs or mice results in a fatal [out]come, but it is only the bovine bacillus wh[ich] can cause progressive tuberculosis in ca[ttle] or rabbits While bacilli of the human t[ype] do grow in the tissues of cattle or rabbit[s] during the first few days even more rap[idly] than do the bovine organisms—the hum[an] bacilli in these animals do not continue [to] grow and to give rise to progressive dise[ase] Thus, the infection brings about in the [tis]sues of cattle and rabbits a change which [is] more antagonistic to the human than to [the] bovine bacilli

THE SOIL The importance of the "soil" [in] determining virulence is particularly str[ik]ing in the case of certain viruses Some v[iruses] reproduce freely only in nerve tissue (ne[u]rotropic viruses) while others grow mo[re] readily in viscera (viscerotropic viruse[s]) If monkeys are inoculated peripherally w[ith] a mixture of viscerotropic and neurotro[pic] yellow fever virus, the viscerotropic vi[rus] multiplies more rapidly than does the neur[o]tropic, whereas the reverse is true if the mi[x]ture is injected into the brains of mice Su[ch] differences emphasize the fact that "t[he] reasons for the differences in virulence b[e]tween the vaccine and virulent strains of t[he] viruses under consideration must be look[ed] for in differences in the normal biochemi[cal] environment of certain specific organs

Evidence strongly suggests that the more virulent the strain, the more resistant it is to the growth inhibitory conditions and substances that prevail at the site of the lesion as the result of inflammatory and immune processes

There are other important processes which are active at the site of infection Phagocytes, antibodies, or antimicrobial drugs do not protect effectively unless they come into contact with bacteria under the proper physicochemical conditions. Moreover, antibodies appear not to function within intact phagocytic cells and may not react with homologous antigens at an acid reaction Wood[16] showed that phagocytosis is much more effective on tissue surfaces than in edema fluid, and antibacterial drugs that are highly effective in the extracellular environment may fail to affect microorganisms within phagocytic cells It is important to develop means of testing the effect of antibiotic drugs upon bacteria under the physicochemical conditions which may obtain within the body, rather than in an artificial culture medium *in vitro*

The Increased Susceptibility of the Diabetic Patient to Infection

It has long been a common observation that the patients with diabetes mellitus, particularly those who are not well controlled, have an increased susceptibility to bacterial infection. The question arises as to whether the metabolic disorders occasioned by the inadequate insulin supply make available to invading infectious agents substances not normally present in significant amounts in the tissues to permit their growth or whether on the other hand, immune defenses are impaired.

There is some experimental evidence to support the hypothesis that bacterial growth is facilitated in diabetics, and the fact that changes in metabolism can permit the growth of invading bacteria was demonstrated by Dubos[9] and others. Animals whose metabolism had been disrupted by treatment with small doses of thyroid extract or dinitrophenol, or by adding to the diet certain substances such as citrate and pyruvate became more susceptible to infection with tubercle bacilli, staphylococci and Friedlander's bacillus Adrenocorticotropic hormone (ACTH) and cortisone have also been shown to facilitate the invasion of certain organisms

TABLE 6 Some Reasons Why Diabetes Predisposes to Infection

1. Subtle endocrine changes may impair body defenses (e g "spontaneous" infections during cortisone therapy)
2. An increased blood sugar level may be less important in permitting bacterial multiplication than is the acidosis which develops in general however acidosis is inimical to bacterial growth
3. Phagocytes in diabetic rabbits retain unimpaired the ability to engulf pneumococci but their bactericidal power for these microorganisms is impaired
4. Evidence has been obtained that the leukocytes of diabetics have an impaired glycolytic power toward bacteria a situation that reverts to normal upon the addition of insulin (see text) thus even the leukocytes can be diabetic

It has been suggested that the whole blood of diabetic patients, regardless of its sugar content, has a weaker bactericidal power than normal blood, and that this loss of activity is related more to acidosis than to any other biochemical disturbance accompanying diabetes Evidence has also been presented that while phagocytes of rabbits made diabetic by alloxan treatment retain unimpaired the ability to engulf pneumococci, they lose some of their bactericidal power for the organisms. There is some indication that the leukocytes of diabetics have an impaired glycolytic power which can be returned to normal by the addition of insulin.[30] "Even the leukocytes are diabetic!"

Immunity and Inflammation: Further Comment

ACIDITY There is suggestive evidence that variations in intracellular acidity may be one of the means by which bacterial cells

are able to bring about the death of certain bacteria, but it is to be remembered that many organisms normally exist within cells and are able to multiply and to cause disease in this situation That the ingestion of foreign material by the cell results in changes in the acidity within the cell was first recognized by Metchnikoff in 1905, when he followed the change of color of litmus particles within the cell [9]

The fact that lactic acid is quite bactericidal at an acid reaction and that lactic acid is an important product of the normal metabolism of phagocytic cells lends further support to the possibility that alterations in pH within phagocytic cells may be bactericidal. Moreover, it is possible that pathogenic organisms are more resistant to changes in acidity than are nonpathogens, this may be one of the factors which permits them to invade—and, as we have seen, the ability to invade is one of the primary factors in virulence In decomposing tissue, for example in necrosis caused by bacterial invasion, fatty acids and other acids are released and accumulate, and they may, in themselves, exert a bacteriostatic and even a bactericidal effect on surrounding organisms

INTRACELLULAR ENZYMES Many investigators have described the presence of intracellular enzymes, and those contained in leukocytes have been intensively studied Leukocytes contain proteases, lipases, esterases, saccharidases, oxidases, and many other enzymes, many of which may attack one or the other part of the bacterial composition Leukocytes are particularly able to produce lysozyme, which has bactericidal and lytic properties Lysozyme appears to be especially abundant in granulocytes

BLOOD FLOW OXYGEN CONCENTRATION, AND IONIC CONTENT Obviously the changes in blood flow and in the permeability of the vascular bed will alter many factors, such as the oxygen supply or lack thereof, as well as the accumulation or dissipation of acid materials which could influence the invasion of microorganisms There is also evidence that the liberation of potassium ion which occurs following destruction of body cells, may be a part of the trigger mechanism which initiates the process of inflammation and the defense against microbial invasion [9]

Effect of Chemical Environment on Toxin Production It is known that, by altering the oxygen or the carbon dioxide tension surrounding a bacterial culture, the organism can be made to grow without producing toxin of the usual strength There are also other properties which the organism may normally possess in the optimal medium, but which may be suppressed or modified by varying the composition of the medium in which the organism is growing Manifestly this is important in considering means by which the body may, by altering the local soil at the site of bacterial invasion, modify the deleterious effect of the microorganisms This represents an additional type of immunity against bacterial invasion

THE FIBRIN BARRIER In the foregoing discussion it was emphasized that acquired resistance can operate not only through a direct action on the infective agent but also by creating around it an environment which is unfavorable to survival of the microorganism, or to its multiplication in sufficient numbers to produce a disease, or by altering its ability to produce its usual toxins The sum total of these influences represents immunity, and *one of the most constant effects of the immunologic response is to accelerate and intensify the inflammatory processes around the infective agent and its products* [9]

Multiple processes assist in eliciting the inflammatory response during infection Among these are the release by microorganisms of substances which are chemotactic for leukocytes, the antigen-antibody as well as allergic reactions with their attendant local production of pharmacologically active substances, the various factors controlling diapedesis, and others

We shall limit the further discussion of the inflammatory defense here to a single

process, that of fibrin deposition On the one hand, the fibrin network provides interlacing pathways throughout the tissue spaces distended with fluid, thus permitting the phagocytes to move readily and to accumulate at the site of infection, on the other hand, the fibrin clot tends to block the various channels and to wall off the infected area, in this way retarding the spread of the invading agent Attention has been called to the fact that when serum is filtered under pressure or diffuses across a fibrin membrane, albumin passes through while the larger globulin molecule is concentrated at the membrane Antibodies, being globulins, do not go through the membrane and remain localized as a protective influence Certain toxins, such as diptheria toxin, diffuse slowly, while most bacterial products do not diffuse through the membrane at all Bacteria themselves tend to be held back by the fibrin membrane, while leukocytes pass readily through it.[9] It is apparent that the presence of the fibrin coagulum is of much importance in determining the chemical and biologic circumstances which exist within the lesion and which may act upon the invading organism Nevertheless, this protective barrier can be destroyed Certain of the invasive capacities of organisms such as streptococci are due to the fact that these organisms have the capacity to produce enzymes which will lyse these fibrin clots and other barriers and permit the organisms to spread Streptokinase and streptodornase are familiar examples

TABLE 7 Some Antimicrobial Defenses of the Body

I Local
- A Fibrin barrier—Albumin traverses the inflammatory membrane but the larger globulin molecule carrying *antibodies* is arrested, to neutralize bacterial products at the periphery of the infection.
- B Leukocytes —Bacteria are engulfed lysis of leukocytes may trigger the local inflammatory response
- C Acidosis—Local products of tissue necrosis result in acidosis which retards multiplication of many microorganisms.
- D Oxygen concentration —The toxin produced by an organism can be altered quantitatively and qualitatively by local alterations in tissue oxygen content.
- E Enzyme mechanisms—The effects of coagulase from coagulase positive staphylococci and of streptokinase and streptodornase from streptococci are important considerations in the local picture the amounts of these enzymes liberated are influenced by tissue reactions.

II General
- A Febrile response —Fever retards growth of some microorganisms
- B Bone marrow reaction —Increased numbers of leukocytes are made available
- C General antibody (immune) response —A complex defensive process
- D General circulatory and endocrine reaction—Infection often flourishes where blood supply is poorest

Systemic Effects of Infection

It is now in order to consider the effects upon the body that are brought about by the bacterial invasion, since these effects are rarely due to the morphologic size, shape, or other characteristics of the organism The organic constituents and the chemical products produced by microorganisms which cause the deleterious effects in the host include a variety of chemical substances such as proteins, lipids, polysaccharides, and many other smaller molecules Moreover, different substances vary profoundly in the manner by which they adversely affect various functions and structures of the body They may represent *endotoxins* or *exotoxins*, and some of the substances are toxic for a wide variety of different cells of the body whereas others are quite specific, such as neurotropic microbes

It is not possible to review in detail the specific processes by which bacteria exert toxic effects upon the body (even if all were known), but a mere listing may suffice to suggest certain of these mechanisms. One form of toxicity is that resulting from *metabolic competitions* A second mode of effect is through *Enzyme toxins*, such as the lecithinase of *Clostridium welchii*. This enzyme

is the chief cause of toxemia in gas gangrene, and may be a factor in death from strangulation obstruction In the presence of calcium it is capable of hydrolyzing lecithin rapidly and sphingomyelin slowly Some enzymes of practical importance are hyaluronidase, produced by many bacterial species, collagenase, which is formed by certain strains of Clostridia and can bring about disintegration of collagen fibers, streptokinase, which is the product of Group A streptococci that converts the protease precursor in plasma (plasminogen) into its active proteolytic form plasmin and thus renders it capable of causing dissolution of fibrin clots, and staphylocoagulase, which is produced by virulent staphylococci

SOME ADDITIONAL PHYSIOLOGIC DISTURBANCES PRODUCED BY ENDOTOXIN The physiologic disturbances produced by endotoxins, which are the factors elaborated by most bacteria of current surgical importance, were reviewed by Thomas,[43] who stated

"The term endotoxin will be used in this review to designate, as a class, the relatively homogeneous group of toxic substances which exist as phosphorus-containing, polysaccharide-protein-lipid complexes in the intact cells of a wide variety of gram-negative microorganisms, or are liberated into culture media during autolysis of the bacteria "

TABLE 8 ENDOTOXINS SOME PERTINENT FACTS

1 The chemical nature of the endotoxin produced has usually little relationship to the morphologic characteristics of the microorganism
2 It is the similarities between endotoxins, rather than the differences, that are most striking The endotoxins of a wide variety of gram-negative microorganisms contain very similar phosphorus-containing, polysaccharide-protein-lipid complexes These materials are liberated into the culture medium upon the death and autolysis of the bacteria
3 The usual effects of the injection of an endotoxin in sufficient dosage are fever, circulatory collapse, hyperglycemia, and leukopenia followed by leukocytosis
4 It is difficult to exclude endotoxin as an etiologic factor in many cases of clinical shock

He emphasized that there has grown up the misunderstanding that gram-negative bacteria produce a wide variety of toxic materials, all differing in their properties as well as their names, that because of the multiplicity of gram-negative bacteria which contain endotoxins, the basic resemblance between the materials is not readily appreciated Yet, endotoxins with similar properties can be extracted from numerous unrelated species of bacteria, and it is the similarity between endotoxins from different bacteria that is remarkable, rather than the dissimilarity

The endotoxins produce in experimental animals a syndrome which is rather typical physiologically and pathologically Although the severity of the reaction produced may vary because of different potency of the particular preparation of endotoxin, the basic pattern of the effects produced in experimental animals by various endotoxins is qualitatively indistinguishable These effects include (1) a profound vasomotor disturbance terminating in shock, characterized by intense, generalized arteriolar constriction, (2) a metabolic disturbance consisting of hyperglycemia followed by hypoglycemia, abrupt depletion of liver glycogen, and excessive amounts of lactic acid in the blood and tissues, (3) high fever, sometimes followed by hypothermia, (4) extreme polymorphonuclear leukopenia, followed by leukocytosis, (5) the production of hemorrhagic necrosis in the substance of rapidly growing tumors, and (6) with sublethal doses, the rapid appearance of a state of resistance against the same and other endotoxins In addition, the endotoxins produce the local and generalized Shwartzman reactions, characterized by hemorrhagic necrosis in the skin and bilateral cortical necrosis of the kidneys when two properly spaced injections of sublethal amounts of endotoxin are administered [0]

VASCULAR EFFECTS It is of particular interest to note that the effects produced by the injection of endotoxins in many animals result in shock, since Fine and his associ-

ates[14] have emphasized that irreversible traumatic and hemorrhagic shock may be due, in part, to the absorption of bacterial products from injured or anoxic tissues Bowel perforation may produce shock (Fig 43)

An extremely virulent form of shock may result from the transfusion of blood contaminated by staphylococci The writer once observed a patient who went into profound shock shortly following the beginning of a blood transfusion The procedure was immediately stopped, the crossmatch checked, and the donor blood cultured The crossmatch proved correct but heavy staphylococcal growth was demonstrated Unfortunately, the patient died a few hours following the transfusion The blood pressure had never risen above shock levels, despite all therapy

EFFECTS OF ENDOTOXIN ON CARBOHYDRATE METABOLISM A striking effect of endotoxin on carbohydrate has been described by many investigators, and there is general agreement that the following events occur with regularity during intoxication by endotoxin The blood sugar becomes elevated within 1 or 2 hours after injection, and hyperglycemia persists for several hours In severely poisoned animals this is followed by extreme hypoglycemia during the terminal stages The liver glycogen becomes greatly reduced within 1 or 2 hours after injection, and the lactate content of the blood and tissues becomes much elevated there may be a concomitant rise and subsequent decrease in pyruvate Evans and Zeckwer,[13] in 1927 found that the effect of endotoxin on carbohydrate metabolism was completely prevented by ergotamine and reversed by insulin They postulated that the hyperglycemia was the result of central stimulation of the adrenals and upon the injection of suspensions of *Escherichia coli* into adrenalectomized rabbits, they observed that instead of hyperglycemia a profound fall in blood sugar levels occurred accompanied by convulsions and death of the animals.

THE PYROGENIC EFFECT OF ENDOTOXIN In



Fig 43 Fatal "bacteremic" (endotoxin?) shock This patient had been sent home on medical therapy for proved amebiasis Several days following discharge he was seized with severe right lower abdominal pain and was readmitted to the hospital in deep shock 2 hours later Laparotomy revealed that at two sites a large patch of right colon wall had disintegrated permitting profuse contamination of the peritoneal cavity with liquid fecal material The involved colon as it appears above was simply exteriorized over a glass rod despite all therapy the shock proved irreversible and he died 6 hours following surgery

fection characteristically causes fever This property of gram negative bacterial endotoxins has been investigated intensively by physiologists for many years According to Thomas,[43] the property of endotoxin which causes fever does not appear to be one which is independent of the properties of the materials which produce the other, more drastic effects such as those upon the cardiovascular system. Substances liberated by destroyed leukocytes may also cause fever

The *mechanism of pyrogen induced fever* has also been the subject of a considerable volume of contradictory literature Suffice it to say that, on the one hand it has been suggested the fever results largely from a reduced rate of heat elimination [44] due to the marked sympathomimetic effect of the endotoxin which results in peripheral vascular constriction and thus a decreased volume of skin vasculature which could result in the usual cooling On the other hand there are those who suggest that peripheral vaso

constriction is of less importance than the actual overproduction of heat, which is considered by them to be the primary factor in fever Evidence which we obtained in postoperative patients suggested that these individuals sweated less readily than they had preoperatively [19]

Leukopenia is followed by leukocytosis Later, *anemia* may appear Wintrobe and his associates[45] published a series of articles dealing with their studies of the anemia which develops in infection In brief, they found that both hematopoiesis and the life span of the individual red cell were diminished Not only were fewer red cells being produced, but also the life span of those that were produced was diminished in length

Central nervous system manifestations are among the outstanding effects of certain endotoxins

Clinical Infections and Their Control

The following questions will be considered in this discussion (1) interpretation of blood cultures; (2) suppuration and drainage; (3) antibiotics· general biologic principles; (4) use of antibiotics in clinical infections; (5) some surgical infections of special importance, (6) use of ACTH and cortisone in infections; (7) chemotherapy of tuberculosis, (8) fungus diseases; and (9) tetanus infection and management

Interpretation of Blood Cultures

In beginning a review of certain clinical infections, together with the physiologic circumstances under which they occur and can be controlled, it is fitting that the positive blood culture be considered first, particularly as it often denotes an infection which is no longer under control and requires the most strenuous treatment

Blood cultures may be positive when overt disease is absent as we have seen Arnold[1] showed that by introducing highly acid chyme into the small intestine the bowel was rendered more permeable to bacteria and that a bacteremia resulted He further showed that certain physiologic alterations in the body, such as adaptations to extrer temperature, whether artificially induced caused by disease, could result in bact remia Similarly, Reith and Squier[35] r ported a study of 293 subjects who had blo drawn for culture at random intervals whi they were performing their usual daily o cupations All had been carefully examin and had had dental x-rays Neverthele positive cultures resulted from 113 of the 2 subjects In 48 the bacteria were consider to be frank contaminants, but in 65 th were considered to have been in the blo at the time of culture Moreover, an increa in positive blood cultures was noted duri the months when upper respiratory tra infections were common As early as 190 Horder[20] observed the fact that the age in most cases of subacute bacterial endo carditis was derived from the mouth, an it has since been amply confirmed that alph streptococci can be found in the blood fo lowing tooth extractions in many patient Murray and Moosenick[32] demonstrate positive blood cultures from patients wit chronic dental disease after they had chewe paraffin for ½ hour Others have indicate that the bacteremia following oral manipu lations is related more to the degree o trauma than to the intensity of oral sepsis

It has been shown that the trauma o operative procedures in the neighborhoo of infections, or during the drainage of in fections, may result in a blood culture positive for organisms identical with those foun in the focus of infection For example Seifert[38] reported that 10 minutes afte surgical drainage of a variety of abscesse positive blood cultures with organisms identical to those in the abscesses were obtained in 45 per cent of his cases, and similar findings have since been reported by others As mentioned earlier, whole body irradiation often results in a bacteremia which may cause death but which can be controlled in considerable measure by liberal amounts of antibiotics The administration of ACTH and cortisone in lobar pneumonia may sup-

press toxic manifestations while the blood culture remains positive

In reviewing 5000 blood cultures at the Los Angeles County Hospital, Kotin[76] attempted to correlate the results of the cultures, where positive, with the clinical situation and with the likelihood that the organism isolated was the cause of the clinical circumstances His conclusion was that, as one might anticipate, the results of blood culture can be definitive in establishing a clinical diagnosis and in determining the prognosis in any given case Past clinical confusion in the interpretation of blood cultures was believed due to several factors (1) an unawareness of bacteremic states during apparent health and in association with minimal trauma (2) preconceived ideas of certain "nonpathogenic" attributes of certain organisms, (3) disregard of special considerations of pediatric bacteriology, (4) lack of correlation with associated diseases in the host, (5) lack of a standard technic of blood culture, and (6) failure to compensate for antibiotic and chemotherapeutic agents Organisms recovered from the blood during health and after minimal trauma were viewed as chiefly and usually 'nonpathogenic" The ability of these bacteria to multiply in the blood stream was usually low their power to produce a septicemic state limited, and their presence transient. Even so these "nonpathogens" may constitute a distinct threat to patients with chronic heart disease particularly those with valvular heart disease

Kotin emphasized that *pediatric bacteriology* as applied to blood culture, requires special consideration, since organisms effectively overcome by adults can be morbid or even fatal to infants in spite of treatment In his series all the cases of *Staphylococcus albus* coagulase negative, were found in cultures from pediatric patients Furthermore gram negative bacilli also were considered to have an increased pathogenicity for infants and children with their limited immune mechanisms Coliform bacilli were present alone or as part of a multiple invasion in 16 cases in children in sufficient numbers to indicate blood stream invasion during life

Another matter of interest was the recurrent finding that a high incidence of positive blood cultures was observed in patients with diabetes and azotemia, especially with regard to the production of disease by facultative pathogens. It was seen above that the immune response may be impaired in both these disease states.

Suppuration and Drainage

Purulent collections of significance must be drained adequately to achieve prompt cure, regardless of what antibiotics are used This fact is well understood, but one important point in technic is often overlooked and leads to disappointment with the results of the surgical management *The drainage tract must remain open until the collection has been evacuated completely and the space obliterated with tissue* A patient we treated illustrated this point very well indeed Following a cholecystectomy he had developed an abscess anteriorly and superiorly, between the dome of the liver and the diaphragm The original surgeon had explored the abdomen and drained the collection yet, all drains were removed within a few days After a few weeks the patient again began to run fever but this time went to another surgeon, who again explored and drained—but again the drains were removed promptly, and signs and symptoms of an abscess recurred When he came to the University Hospital, almost 18 months after the original biliary surgery he was febrile, he had lost a great deal of weight, he was getting a divorce from his wife, he had lost all confidence in doctors, and he was convinced he would never get well However we too drained the huge space, partially filled with pus and necrotic debris, but when the packing was removed postoperatively a 25 cc Foley catheter was introduced into the space When weeks later the space had closed to the 25-cc size the bag was deflated, but the catheter was still left in place and the

space was irrigated with streptokinase-streptodornase until it had become obliterated Following this the patient's "psychosis" disappeared, he gained weight, he got his job back, paid his bill, effected a reapproachment with his wife, regained confidence in doctors—and turned out to be a very pleasant person There was no recurrence

Antibiotics: General Biologic Principles

The biochemistry of antibiotics has come to consitute a vast field of endeavor, and some of the important papers in this field have been reviewed by Duggar and Singleton [11]

SYNERGISM IN ANTIBIOTIC THERAPY. The specific use of antibiotics under various circumstances will be further discussed below Before proceeding, though, certain conceptual considerations should be examined, and the first of these is the matter of whether or not *synergism* exists between different antibiotics On the basis of their studies, it was concluded by Romansky and his associates[36] that antibiotic combinations, *in vitro,* exhibited synergistic action against some strains of bacteria Jawetz and Gunnison[23] concluded that it was not an easy matter to prove synergism between antibiotics—that is, to demonstrate a large increase in the rate of early bactericidal action and the rate of cure of infections beyond that obtainable by simple additive effects of the agents Regarding the value of using antibiotics in combination (bearing upon synergism) Dowling, Lepper, and Jackson[7, 8] offered the following suggestions First, a single antibiotic can be used effectively in most infections caused by a single organism and, moreover, one of the broad spectrum antibiotics (Aureomycin, oxytetracycline, or chloramphenicol) may be employed in mixed infections of the peritoneum that follow the rupture of a viscus Occasionally a single antibiotic may be used in a mixed infection in which it has been proved to be of value, for example, penicillin may be used in the treatment of lung abscess

Second, in certain infections the value combinations of antibiotics has been prov both in the laboratory and the clinic Th group includes streptomycin plus Aure mycin, chloramphenicol, or oxytetracycli in brucellosis, penicillin plus streptomyc in enterococcal endocarditis, and penicill plus Aureomycin, chloramphenicol or ox tetracycline in serious staphylococcal in fection in which the organism is resista to any of these antibiotics used alone I these infections the proper combinatio should be used from the start of therapy an when such a combination succeeds whe the individual drugs have not succeeded, on might justifiably say that synergism ha been demonstrated Third, if the infectio does not fall into either of these classe the *in vitro* effect of combinations of variou antibiotics should be studied, and the combination showing the greatest synergisti effect should then be used Fourth, thes authors noted that antibiotics may be divided into two groups Those in Group are primarily bactericidal and they ar penicillin, streptomycin, bacitracin and neomycin, those in Group 2 are primarily bacteriostatic and they are Aureomycin, chloramphenicol, and oxytetracycline

Clearly, it is most difficult to prove synergism conclusively, since so many of the drugs which might be used in combination have individually a broad range of effectiveness and because various physicochemical circumstances have, as we have seen previously, a profound effect upon the capacity for bacteria to multiply Furthermore, synergism *in vitro* may by no means represent the same circumstances which exist in the human body, where truly controlled data are difficult, if not impossible, to obtain

ANTAGONISM As noted, the introduction of a wide variety of active chemotherapeutic agents has led to the use of combinations of these agents, with the objective of obtaining

additive or synergistic effects Nevertheless, there is also evidence that under certain circumstances antimicrobial agents may, when combined, actually have an *antagonistic* action Lankford and Lacy[27] studied the *in vitro* bacteriostatic action of Aureomycin penicillin and Aureomycin streptomycin mixtures on staphylococci and concluded that synergistic, indifferent, or antagonistic effects could be obtained, depending on the relative concentrations of the two drugs Spicer[40] also demonstrated *in vitro* an antagonistic effect between certain antibiotics, and he concluded that if an antibiotic to which a bacterial strain was only moderately sensitive were combined with one of high activity, the action of the latter might be impeded.

Again, as with the question of synergism it is not easy to prove in human beings the existence of antagonism between two antibiotics Moreover to emphasize once again the presence of antagonism in the test tube does not by any means represent the circumstances which may exist in the body

RESISTANCE OF MICROORGANISMS TO ANTIBIOTICS Not many years after penicillin was available it became apparent that certain strains of bacteria were becoming penicillin resistant Among the first organisms to exhibit such a resistance were the gonococci, but soon the staphylococci[16] were proving refractory to treatment in many instances streptococci showed less capacity to develop resistance For example when penicillin first came into general use in the United States (1943–1945) 80 to 90 per cent of the strains of staphylococci encountered were quite sensitive to this agent, by 1955 however this therapeutic advantage had been greatly diminished for now in many hospitals from 75 to 85 per cent of the staphylococci isolated from wound and other infections were found resistant to penicillin. Spink[41] reported that the case fatality rate for micrococcal septicemia before the advent of sulfonamides was over 80 per cent and that it was slightly less than this during the sulfonamide era In the years 1942 to 1944 just after penicillin was introduced, the fatality rate fell to 28 per cent but by 1955 it had risen again to 50 per cent, regardless of the antibiotic used Similarly, Howe[21] reported a progressive increase in the incidence of wound infections from 1 09 per cent in 1949 to 3 98 per cent in 1953 following "clean" operations

The simplest explanation is that the widespread use of penicillin has resulted in a gradual evolvement of mutant strains which can multiply in a medium containing penicillin While it has been in the treatment of staphylococcal infections that resistance has constituted the most serious cause for concern—in view of the high incidence of staphylococcal infections and the fatal issue of staphylococcal septicemia in many cases—other bacteria exhibit diminished sensitivity in varying degrees Moreover it is to be remembered that, whereas resistant strains of bacteria are on the increase, the viruses and fungi have never been effectively controlled by antibiotics

The development of resistance may take place even while the patient is under treatment with antibiotic For instance it has been noted that a strain of alpha streptococci may increase more than 1000-fold in resistance to penicillin during only a few weeks[illegible] though streptococcal resistance is uncommon. Another important clinical manifestation of resistance is that in which the original bacterium was sensitive to the antibiotic, but when this was suppressed other organisms which were originally present in small numbers overgrow the predominant organism A common example of this is the urinary tract infection in which a Proteus replaces *Escherichia coli* while the patient is receiving one of the tetracyclines. Another example which will be discussed in somewhat greater detail subsequently is that of micrococcal dysentery (pseudomembranous enterocolitis), which may appear during the course of treatment of some remote infection Most of the other micro

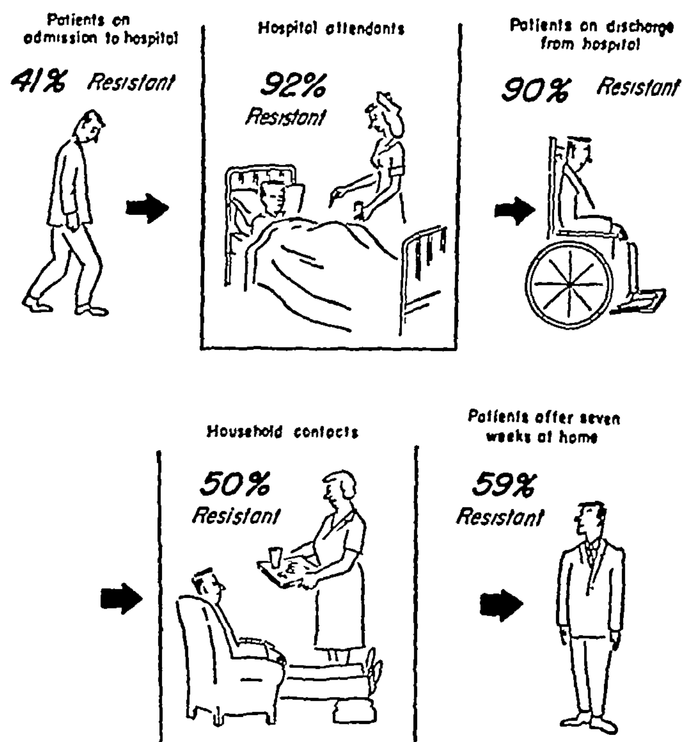


Fig 44 The acquisition of resistant organisms by the patient during hospitalization Percentage of chlortetracycline-resistant micrococci cultured from the upper respiratory tracts of patients, hospital attendants, and household contacts (From Dowling, H F, Lepper, M H, and Jackson, G G Clinical significance of antibiotic-resistant bacteria J A M A, **157**: 327, 1955)

organisms in the intestine are suppressed by the use of the antibiotics, and the micrococci (*Staphylococcus aureus*) that are resistant to the antibiotic which is being administered are allowed to grow out in the bowel in enormous numbers

In general, more resistant strains are encountered in the hospital population, including both patients and hospital attendants, than are encountered in the population at large, unquestionably due to the large amounts of antibiotics which are used in hospitals In Figure 44 are presented the changes in the number of resistant micrococci encountered under various circumstances It will be seen that the patient harbored far more resistant organisms on discharge from the hospital than on admission Such resistance applies both to penicillin and to chlortetracycline (Aureomycin), though in different degrees

As pointed out, in contrast to the increased development of resistance by staphylococci, streptococci have not ex ited this phenomenon in a parallel fash though streptococcal resistance is not i Berntsen[2] found that there was no sig cant change in the penicillin susceptib of alpha hemolytic streptococci (*Stre coccus viridans*) isolated from patients v bacteremia and bacterial endocarditis was noted that the absence of change such an ubiquitous organism as the al streptococcus emphasizes that the prob of the increased prevalence of penicillin sistant micrococci does not necessarily r resent a phenomenon with general appli tion to all pencillin susceptible microl species

Cross-resistance to antibiotics has e further limited the effective antibiotic mamentarium In brief, it has been fou that resistance to one antibiotic may transferred to resistance to other antibiot though by no means to all antibiotics F thermore, the matter of the development resistance varies considerably from one a tibiotic to another In a report by Haig Wilcox, and Finland,[18] serial subcultu were carried out in media containing stre tomycin, neomycin or no antibiotic, and t resulting bacterial strains were tested sensitivity to both streptomycin and ne mycin and also to six other antibiotics T organisms which had been transferred antibiotic free media retained their origi sensitivity to both antibiotics The repeat subcultures in media containing streptom cin or neomycin resulted in increased resis ance to the homologous antibiotic in mo but not in every instance The developme of neomycin resistance was quite regular associated with a significant increase in r sistance to streptomycin, but the reverse d not occur so often, that is, neomycin resis ance developed irregularly and was of rel tively low degree in the organism which ha become streptomycin resistant

Use of Antibiotics In Clinical Infectio

THE COMMONLY USED ANTIBIOTICS The su fonamides have largely given way in m

portance to antibiotics Thus the sulfonamides, while important in some instances, will only be touched upon in the subsequent discussion

Penicillin This agent represents perhaps the most important single advance in therapy against infection, and it became available to the general medical profession in 1944. It is bacteriostatic in threshold doses (being bactericidal in higher concentrations), it is relatively well absorbed when given orally, it is rapidly absorbed from intramuscular depots, and it is extremely rapidly excreted by the kidneys, a factor which results in marked fluctuation of blood levels Penicillin is quite soluble and readily penetrates most body tissues, with the exception of the brain, other nervous tissue, and fat. Its precise effect upon the microorganism is obscure, but it appears to cause some subtle derangement of protein synthesis within the bacteria

Penicillin has a marked selective affinity for gram positive organisms and spirochetes. It is quite effective against *Neisseria gonorrhoeae* and *Neisseria intracellularis*, but it is not effective against gram negative, mycobacterial, rickettsial, protozoal, most viral (exceptions, psittacosis and ornithosis) and fungous infections It is not as effective in controlling mixed infections as it is in controlling monobacterial infections, largely because certain bacteria have the power to produce an enzyme, *penicillinase* which inactivates the drug. Resistance is most commonly encountered in the staphylococcal and nonhemolytic streptococcal species, and least often in Neisserian organisms

The maintenance of a constant blood level of penicillin is not necessary for satisfactory treatment Organisms exposed to bacteriostatic concentrations of penicillin cease multiplying and are damaged in such a way that they do not resume normal growth for several hours after the drug has been stopped The time required for postpenicillin recovery varies from strain to strain with the concentration of penicillin used, and with the duration of the exposure One important factor in the effect of penicillin is its accumulation in inflamed tissue

For the most effective action, penicillin is given intramuscularly or intravenously in adequate dosage, but the oral route is popular with the patient and the expense involved is no longer excessive, as it once was. To produce comparable blood levels, the oral dose must be from three to five times the intramuscular dose Since different individuals show considerable variation in the absorptive capacity for penicillin, the daily oral dose should probably exceed 250,000 units to be certain that absorption will be satisfactory Penicillin may be administered by nebulizer, and it has been used locally in joints, pleural cavities, open wounds and around the base of carbuncles

Streptomycin Streptomycin was isolated from a soil actinomyces (*Streptomyces griseus*) by Waksman and his associates[37] in 1944 This agent was for a time the major antibiotic weapon against gram negative organisms and is still a major weapon against the tuberculosis organism It possesses both a bacteriostatic and a bactericidal action, depending upon its concentration. Because it is not absorbed from the gut, parenteral administration is required to insure adequate serum and tissue levels, whereas it provides an excellent agent for sterilizing the bowel prior to intestinal surgery when it is given by mouth

When streptomycin is used intramuscularly the drug passes readily from the blood stream into the peritoneal cavity and pleural fluid. Since diffusion of streptomycin into the cerebrospinal fluid (as with penicillin) does not readily occur in normal patients, it is best to employ the intrathecal administration of from 1 to 1.25 mg. per kg of body weight per day to insure proper levels in meningitis Nevertheless, there is evidence that in the presence of meningitis streptomycin given intramuscularly can pass more readily into the cerebrospinal fluid.

The *dosage* of streptomycin is usually on the order of from 1 to 3 gm. per day in divided doses. This dosage should be

duced within a few days, to diminish the risk of VIIIth nerve damage and deafness To produce high sputum levels of streptomycin, it may be given by nebulizer in doses of 100 mg per day

Dihydrostreptomycin This relative of streptomycin was introduced in 1948 as a less neurotoxic agent than streptomycin Unfortunately, it was soon shown that *qualitatively* it had the same toxic effects as did streptomycin, although the *quantitative* effects were less That is, if given long enough and in sufficient dosage, dihydrostreptomycin may also cause VIIIth nerve damage, but not as readily as streptomycin

Dihydrostreptomycin is effective against a variety of gram-negative and gram-positive bacteria, being quite similar to streptomycin in this respect, it is used intramuscularly but not intravenously This agent is considered to be synergistic with penicillin, and a useful combined dose is 0 5 gm with 400,000 units of procaine penicillin daily

Aureomycin (*chlortetracycline*) This drug was one of the first broad spectrum antibiotics to be isolated, and was reported by Duggar[10] in 1948 Isolated from a soil actinomycete (*Streptomyces aureofaciens*), it is effective against many gram-positive and gram-negative bacilli, all species of rickettsia, certain viral agents, and protozoa Of further interest, the feeding of this agent to farm animals may result in larger animals

Aureomycin is not effective against tuberculosis infection in man, nor against most strains of Proteus and Pseudomonas It is supplied in 250-mg capsules for oral administration, and in 100-mg vials for intravenous use The intravenous dose is approximately one-fourth the oral dose, and it may be given in saline over a 30-minute period at 12-hour intervals It often causes an inflammation of the vein, particularly will thrombophlebitis result from repeated injections in the same vein, and thus the oral route is used when possible One may prefer to give the medication with some foodstuff, to diminish the irritation and likelihood of nausea and vomiting and diarrhea which m infrequently develop, though this is not us ally a major complication The total dosa for adults varies from 1 to 4 gm daily, d pending upon the situation, and is usual divided into 250-mg or 500-mg doses F children, a satisfactory dosage is from 1 to 25 mg per kg of body weight per d in divided doses given with some swe which will make the taste more palatab Aureomycin, unlike streptomycin and pe icillin, readily traverses the blood-bra barrier and enters the cerebrospinal fluid well as pleural fluid It is irritating local and should not be given intrathecally, i trapleurally, or by nebulization[28]

Chloromycetin (*chloramphenicol*) Th drug was isolated from *Streptomyces ven zuelae* in 1947[12] As with Aureomycin, exerts a bacteriostatic but not a bacteric effect It is particularly used in the trea ment of typhoid fever, the rickettsial di eases, and certain of the gram-negative ur nary tract infections It is of use in tl treatment of pertussis in brucellosis whe given in combination with streptomyci and in relapsing fever, bacillary dysenter and *Hemophilus influenzae* infections

Chloromycetin is supplied in 250-m capsules for oral administration, and readily absorbed from the gut The recon mended initial dose is 60 mg per kg of bod weight, with a maintenance dose of fro 0 25 to 0 5 gm every 3 to 6 hours durin the febrile period, and for 5 to 10 days there after For infants and children a satisfac tory dose is from 100 to 200 mg per kg o body weight per day, given in divided dose

Terramycin (*oxytetracycline*) Terramy cin is an active antibiotic isolated from th metabolic products of *Streptomyces ri mosus* It has a wide range of activit against both gram-positive and gram-nega tive bacteria, and it is rapidly absorbe from the gastrointestinal tract, producin significant and continuous blood concentra tions for periods up to 6 hours The princip route of excretion is by the kidneys, and i appears in the urine in an active state How-

ever, relatively large amounts of Terramycin are also excreted in the feces The drug is widely distributed throughout the body

In general, Terramycin has a spectrum range similar to that of Aureomycin For oral use, capsules of 250 mg are available and the drug may be given in a flavored syrup for children It may also be given intramuscularly and intravenously, and is available in vials containing 100 mg, 250 mg. and 500 mg respectively The latter amounts are easily given intravenously and the former intramuscularly A satisfactory dosage in children is from 6 to 12 mg per kg. of body weight per 24 hours given in two divided doses Terramycin does not diffuse readily into the cerebrospinal fluid

Erythromycin A particular advantage of this agent is that it is effective against some strains of bacilli, especially staphylococci, that are resistant to penicillin *Micrococcus pyogenes* (*Staphylococcus aureus*) is now commonly insensitive to penicillin, streptomycin chlorotetracycline (Aureomycin) and oxytetracycline (Terramycin) and has produced fatal cases of ileocolitis (pseudomembranous enterocolitis) In uncontrolled infections due to this organism erythromycin has in many instances proved to be of great value In fact many have considered it advisable to reserve erythromycin for staphylococcal infections which do not respond to the other antibiotics

A daily dose of from 20 to 25 mg per kg. of body weight is recommended for the average adult patient when the oral dose exceeds 400 mg. every 6 hours gastrointestinal irritation may occur The smallest oral daily dose which will maintain adequate concentration in the serum is approximately 300 mg. Erythromycin does not readily enter the cerebrospinal fluid but does appear to enter ascitic and pleural fluid The drug may be given orally, intramuscularly and intravenously The *oral route is preferred for* patients with enterocolitis

Tetracycline (*Achromycin, Tetracyn*) Tetracycline is similar in chemical structure and action to Aureomycin and Terramycin Finland and his associates[16] studied cross resistance between tetracycline (Achromycin), chlortetracycline (Aureomycin) and oxytetracycline (Terramycin) They found almost complete cross-resistance among the three tetracycline analogues *in vitro*

One advantage of tetracycline is that gastrointestinal symptoms appear to be somewhat less common and worrisome than those due to Aureomycin and Terramycin

Neomycin This drug is relatively effective against Proteus, and has had a particularly important use in sterilization' of the intestine in association with large bowel surgery it is only very slightly absorbed from the intestinal tract. Poth[33] has stated that the injection of neomycin in saline into a loop of bowel can result in sterilization of the bowel contents within minutes We have used it in this manner when unanticipated colon resection was required, but we have not checked its effectiveness by culturing the colon content.

The chief disadvantage of neomycin—and a fact which has greatly limited its use—is its nephrotoxicity and ototoxicity Granular casts regularly appear in the urine during and following treatment and the blood urea nitrogen rises in patients having an elevated blood urea nitrogen level at the beginning of therapy[28] Impairment of the VIIIth nerve may result in total deafness, a complication which may not appear until after the drug has been stopped it has been stated that treatment for as long as 4 days may produce deafness following parenteral administration of neomycin Therefore, while it is justifiable to use neomycin in the presence of Proteus septicemia which does not respond to other drugs, the dose administered should probably not exceed 1 gm. per day

Polymyxin This drug is an effective agent against many gram negative organisms including with the exception of Proteus, many which are resistant to streptomycin In fact organism resistance is not a major problem Unfortunately though its nephrotoxicity limits its widespread clinical use When it

is used, the dosage should not be in excess of 2 5 mg per kg of body weight per day for more than 5 days It is one of the most potent drugs available against pyocyaneus infections It may be applied topically in 1 per cent concentrations, and it is markedly effective against gram-negative organisms if dead tissue is not present in abundance Not absorbed into the circulation following oral administration, it effectively decreases the gram-negative flora of the bowel

Bacitracin Johnson, Ankar, and Meleney[24] described this agent in 1945 Its antibacterial spectrum closely resembles that of penicillin, but is not destroyed by bacteria which produce penicillinase It is used chiefly as a local agent against coccal infections Systemic use is limited because of its markedly nephrotoxic properties and, actually, the drug has never been widely used

Sulfonamides Sulfonamides are not considered antibiotics, but it is desirable to mention their value The former widespread use of these agents has largely been superseded by antibiotics since, for the most part, the effect of sulfonamides is nullified by the products of tissue necrosis Moreover, sulfonamides act merely as bacteriostatic agents Nevertheless, sulfathalidine and sulfasuxidine are still commonly used for preoperative preparation of the intestinal tract for colon surgery, and sulfadiazine is still used in the treatment of Shigella infections Gantrisin is a sulfonamide that is effective in the treatment of many urinary tract infections, renal complications are rare and its solubility is high at the usual pH range of urine

Finally, where expense is a deciding factor, sulfonamides will frequently suffice in place of the often expensive antibiotics

SELECTION OF AN ANTIBIOTIC Ideally, the sensitivity of the organism or organisms in purulent material should routinely be determined and the most effective available antibiotic employed (Fig 45) In practice, however, this is not feasible in a very considerable number of circumstances, particularly those in which antibiotics are employed outside of hospital practice Nevertheless, is important in serious or prolonged chron infections to study the flora with respect the antibiotic sensitivity of the various mi croorganisms and then to employ the ind cated antibiotic in sufficient dosage to e radicate the organism Selection of t proper agent is particularly important view of the ever increasing antibiotic resi tance of many strains of bacteria, for it obviously advisable to limit the develo ment of resistance as much as possible

In general, the following guide would ap pear to be a useful one Penicillin should b used in the treatment of acute gram-positiv coccal, clostridial, and actinomycotic in fections It is cheap and virtually nontoxi Aureomycin, Terramycin, Achromycin, c gantrisin may be used for infections of th urinary tract which are usually caused b organisms of the coliform group Erythro mycin and novobiacin, which are effectiv against many strains of staphylococci tha are resistant to penicillin, should perhap be reserved for use in those infections whic cannot be controlled by other means Strep tomycin and drugs of the tetracycline grou should be used for diseases caused by gram negative bacilli that may be resistant t penicillin Chloromycetin (chloramphen col) is an effective drug for typhoid fever Penicillin and Aureomycin are particularly effective in spirochaetal diseases Tetracy cline derivatives are the agents of choice in rickettsial disease

Again, though, a determination of organism sensitivity decreases the delay in bringing the disease under control, it reduces the expense to the patient, and it reduces the incidence of resistant strains that result from indiscriminate antibiotic usage

Some reasons why infections fail to respond are (1) the causative organism was not among those isolated, (2) resistant bacterial mutants are present, (3) the dosage is inadequate, (4) the original susceptible flora has been replaced by a more resistant one, and (5) there exist mechanical or anatomic barriers limiting access of the drug

	TUBERCLE BACILLI	GRAM POSITIVE ORGANISMS	MENINGOCOCCI GONOCOCCI	GRAM NEGATIVE BACILLI	RICKETTSIA LARGE VIRUSES	AMEBAE
BACITRACIN ERYTHROMYCIN						
PENICILLIN						
STREPTOMYCIN NEOMYCIN						
THE TETRACYCLINES CHLORAMPHENICOL						
POLYMYXIN						
FUMAGILLIN						

Fig 45 The diagram emphasizes some therapeutic indications for the various antibiotics In addition novobiocin oleandomycin ristocetin and vancomycin are used primarily against staphylococci and nystatin (mycostatin) is effective against Candida albicans (monilia) (From PULASKI, E. J In *Physiologic Principles of Surgery* edited by L M Zimmerman and R Levine Philadelphia W B Saunders Company 1957)

to the site of infection such as in an abscess or in the valvular vegetations of subacute bacterial endocarditis

Some Surgical Infections of Special Importance

STAPHYLOCOCCAL INFECTIONS Whereas before 1900 tuberculosis constituted a major cause of death due to infection and whereas during the first half of the twentieth century pneumonia became in turn the major cause of death due to infection these two diseases have now been reasonably well controlled by specific chemotherapy and other measures Certainly pneumococcal pneumonia does not occupy anywhere near the prominent position it once did On the other hand it is increasingly apparent that staphylococcal infections have now claimed at least in hospitalized patients, the major position as a cause of death due to infection This fact was supported by a report from the Montreal General Hospital, where DeVries and Pritchard[4] made cultures routinely of heart blood, cut surfaces of lungs, and other infected areas of all patients coming to autopsy In a series of 213 such cases observed from October 1953 to May 1954, these cultures yielded *Micrococcus pyogenes* (*Staphylococcus aureus*) in 87 cases *Diplococcus pneumoniae* in 4, *Klebsiella pneumoniae* in 3 and *Streptococcus pyogenes* in 1 All but 7 of the 87 staphylococcal strains were obtained from the heart blood or lungs or both. These findings were in striking contrast to those obtained in 311 autopsies done at the same hospital in 1950, when the records showed only 3 cases of bronchopneumonia

and 2 cases of septicemia due to staphylococci However, cultures were not done routinely during that period It was notable in the more recent series of cases that only 3 patients were admitted to the hospital with the diagnosis of staphylococcal septicemia, and that the majority of the infections were considered to be terminal infections in patients with chronic debilitating diseases, that is, the infections were acquired within the hospital In support of this view, 61 per cent of the strains of staphylococci belonged to *phage Group 3, the most common group of staphylococci found in carriers in hospital personnel*

Micrococcal pseudomembranous enterocolitis a complication of antibiotic therapy A condition which has been termed pseudomembranous enterocolitis has recently emerged as one of the complications of antibiotic therapy, as previously mentioned This condition, which is characterized by replacement of the mucosa of a considerable portion of the intestine by a gray fibrinous membrane, may follow extensive burns and gastrointestinal hemorrhage, it may also follow operations which do not involve the abdomen, but most often it follows gastrointestinal surgery Finney[17] apparently reported one of the earliest cases in 1893, when a fatal enterocolitis developed in a patient 10 days after a pyloric resection and gastroenterostomy for benign pyloric obstruction In 1948 Dixon and Weismann[5] reported from the Mayo Clinic that pseudomembranous ileocolitis had been encountered at autopsy in a wide variety of both medical and surgical conditions The clinical picture associated with this condition was that of rapidly progressing circulatory collapse with fever, diarrhea, abdominal distention, and vomiting—characteristics of endotoxin poisoning Profound circulatory collapse occurred suddenly and proved resistant to the usual supportive measures Autopsy revealed the replacement of segments of the mucosa of both small and large bowel by a gray fibrinous membrane which on microscopic examination was seen to consist of necrotic cellular debris, leukocy and bacteria The submucous layer markedly edematous and hyperemic, an more recent studies it has been found contain great numbers of micrococci In viewing 23 cases of pseudomembranous terocolitis as a fatal postoperative com cation, Speare[39] emphasized that increasing incidence of this condition surgical patients appeared to be due to emergence of antibiotic resistant strains *Micrococcus pyogenes* In most of the rec reports, pure cultures of strains of *M py genes* resistant to penicillin, streptomy chlortetracycline (Aureomycin) and o tetracycline (Terramycin) have been fou in the stools and intestinal lesions of th patients, the normal intestinal bacte flora has been either absent or diminish Thus, the consensus appears to be that cause of this complication is a massive in sion of the intestinal mucosa by the an biotic resistant strains of *M pyogenes* the absence of the normal bacterial flo In the patients reported by Speare, the cli cal findings were quite similar in all cas There usually occurred some abdominal pa and nausea 1 or 2 days after a successful executed operation There followed a m rise in temperature, associated later with moderate or profuse diarrhea Thereaft the patient's condition rapidly deteriorate and a state of shock resistant to blood tran fusion and the other usual supportive mea ures intervened At autopsy, lesions invol ing large areas of the gastrointestinal tra were found, there being segments of ye lowish gray and grayish brown diphtheri membrane adhering to the denuded mucos It was considered possible that this w caused by the intense hyperemia and vasc lar engorgement of the underlying stroma

The mucosa becomes necrotic, peels o and with the cellular debris and bacter forms a diphtheritic membrane Of the 2 patients reviewed by Speare, 19 had di and, of the 3 patients who survived, 2 h been treated with erythromycin, one of t few effective agents against *M pyoge*

under these conditions Novobiocin is also now available for use against this organism

Use of ACTH and Cortisone in Infections

It is not the purpose to review in detail specific regional infections such as peritonitis, osteomyelitis and others, nor is it desirable here to do so However, the use of ACTH and cortisone in conjunction with antibiotics in the management of certain infections should be mentioned The rationale of such therapy perhaps originated with the demonstration by Kass, Ingbar, and Finland[23] that the fever and toxic symptoms of pneumonia were abolished by these drugs even when the blood culture remained positive for pneumococci There was no evidence of a bactericidal effect, and the date of the appearance and the magnitude of the rise in antipneumococcal antibodies and cold agglutinins were unaffected by ACTH and cortisone. Furthermore, the rate of resolution of consolidated lobes was not accelerated.

This report created much interest in the effects of ACTH and cortisone in experimental and clinical infections, since in them an agent had been found which apparently reduced the effect of bacterial toxins on body cells, while allowing the bacteria to continue to multiply Somewhat later Mogabgab and Thomas[31] reported their studies concerning the effect of cortisone on experimental infection with Group A streptococci in rabbits. These workers injected Group A streptococci into the skin of rabbits some of which were treated with cortisone in doses of 50 mg. per day and others kept as controls without cortisone therapy In the treated group a fatal septicemia developed in all animals whereas in the controls who received the same dose of bacteria but no cortisone there were no deaths

Since these early studies so called "spontaneous" infections have been reported from time to time in patients receiving cortisone therapy It has been suggested that such spontaneous infections are quite possibly due to a flare-up of foci which are ordinarily suppressed by the patient's defense mechanisms, but that they may be the result of invasion by "nonpathogens" in hosts whose defense mechanisms have been impaired by the hormone In brief cortisone may so alter the defense mechanism of inflammation that bacteria are provided with suitable circumstances under which to multiply and spread —and as has been seen, pathogenicity consists largely of the ability of the individual bacteria to multiply under the physicochemical circumstances in which they find themselves it is not necessarily due to the specific toxin which the bacteria normally produce

ACTH AND CORTISONE IN PERITONITIS In view of these earlier studies, Boling and his associates[3] examined the use of ACTH and cortisone in the management of generalized peritonitis It was their thought that if in severe cases a block could be temporarily interposed between the effects of the toxins and the host then the defenses of the host might not be overwhelmed and time would be thus gained to permit large doses of antibiotics to reduce the growth of the organisms Their observations suggested that the use of ACTH or cortisone, in conjunction with chemotherapy, might be of significant value in the preoperative and postoperative management of patients with generalized peritonitis Nevertheless, these workers were careful to point out that the ACTH and cortisone could completely mask serious complications and, further that these agents had no inhibitory effect upon the growth of the pathogenic organisms

Subsequent studies by others have failed to establish the clinical value of this form of therapy Moreover, in two subacute experimental bacterial infections in mice, Jawetz[22] found that even very small amounts of cortisone markedly interfered with the therapeutic effectiveness of antibiotics The phenomenon was observed not only when the animals were pretreated with cortisone but also when the administration of both cortisone and antibiotic was started several hours after infection. The magnitude

of this effect depended upon the severity of the infection, as determined by the number of bacteria inoculated and on the dose of the antimicrobial agent It was greatest when the result of antimicrobial therapy without cortisone was subcurative With the administration of a large excess of antibiotic beyond the curative dose, the reduction of therapeutic effect by cortisone was no longer evident

These hormones have aided in some cases of brucellosis [42]

Chemotherapy of Tuberculosis

One of the most gratifying milestones in recent years has been the relative effectiveness of chemotherapeutic agents in the management of tuberculosis Among other things, it has made possible widespread application of resectional surgery in parenchymal pulmonary disease Prior to the advent of streptomycin, the incidence of serious postoperative complications such as bronchopleural fistula and spread was so great that it was relatively uncommon to resect portions of the diseased lung Happily, streptomycin, aided by the concurrent administration of *para*-aminosalicylic acid (PAS), caused the more exudative portions of the disease to regress, until isolated foci were present which could be safely excised In the beginning a dosage of 1 gm of streptomycin and 12 gm of PAS was used daily, but later the schedule was altered to consist of 1 gm of streptomycin twice or thrice weekly and 12 gm of PAS daily A large number of patients have now been treated both by the daily and by the twice weekly streptomycin programs, and statistical analysis has established that they are quite similar in therapeutic efficacy There is some evidence that the development of streptomycin resistant strains is retarded by the administration of PAS Streptomycin toxicity, particularly VIIIth nerve damage, is much reduced when the amount of the drug given (now, usually dihydrostreptomycin) is only 2 gm per week

Isoniazid This drug became available to the medical profession in May, 1952 Studies have shown that isoniazid is an effective agent against tuberculosis As with streptomycin, though, the tubercle bacillus may develop resistance to the drug The toxic effects of isoniazid involve the nervous system, the most frequent being twitching of the muscles, insomnia, and headache These findings may disappear when the drug is withheld—and often even if it is continued—and they are rarely serious enough to interfere with therapy Some patients exhibit changes in temperament which may be characterized by irritability or euphoria, and these subtle changes in personality may be the commonest toxic manifestations of all The dosage of isoniazid is generally estimated on a body weight basis, and usually ranges from 0 15 gm to 0 3 gm per day There is no question that the drug represents another important advance in effective chemotherapy against tuberculosis Where the organism is particularly sensitive to this agent the patient may show a striking and prompt improvement that is reflected in an increased appetite, weight gain, and in general clinical condition It not infrequently happens that the bacteria recovered at surgery following isoniazid therapy and, for that matter, at times following streptomycin therapy, fail to multiply and to exhibit pathogenicity when injected into guinea pigs

Frequently, now, isoniazid, streptomycin, and PAS are used concurrently

Fungous Diseases

At the present time surgery is used only sparingly in fungus infections For example, sinuses due to actinomycosis may be excised, along with the administration of heavy doses of antibiotics, particularly penicillin. Blastomycotic lesions may be excised from the skin or as isolated lesions in the lung Histoplasmosis may produce lesions in the lungs which are sufficiently localized to be excised and which, indeed, are usually excised with the thought that they [illegible] pulmonary tuberculo

made in the course of postoperative examination of the tissues Even so, fungus diseases do not often present indications for surgery *Antibiotics* are not particularly effective against fungi, but specific chemotherapy such as stilbamidine is proving to be relatively effective. Penicillin is frequently used against actinomycosis, but the results leave much to be desired Also, there is available at this time no treatment that is consistently effective against histoplasmosis Yet, therapy is improving.

There is some evidence that fungus infections are increasing as the result of antibiotic therapy, in that bacterial growth in the alimentary tract, particularly the mouth is suppressed by the broad spectrum antibiotics. Fungi such as monilia (*Candida albicans*) may be allowed to grow rapidly whereas normally the bacterial flora suppresses these organisms Moreover, while moniliasis is usually not significant, this infection is occasionally serious, pulmonary infections may occur and fatal endocarditis has been reported

Tetanus Infection and Management

Tetanus is a condition in which there is local spasm or general convulsive contractions of voluntary muscles due to the effect of the specific *exotoxin* produced by *Clostridium tetani* The organism thrives best in an anaerobic medium and may be a frequent contaminant of dirty wounds It is saprophytic and is commonly found in the feces of most mammals, particularly horses and cattle in man, it is often found in the intestinal tract of individuals who have daily contact with domestic animals Tetanus organisms may exist in the tissue for long periods of time without causing disease, but should the tissues be damaged by mechanical or chemical means or by other bacterial infection to produce a suitable medium in which tetanus bacilli may grow, the spores are activated and the bacilli multiply and produce a powerful exotoxin

The tetanus bacilli may enter the body in a variety of ways, usually through a wound, but entrance may follow extraction of teeth or quite trivial injuries, and it has been known to follow childbirth The period of incubation may vary enormously and, whereas it may produce active disease within a relatively few days (it has been reported within 24 hours of the injury), it may be many weeks or even months following the initial injury before tetanus develops Indeed, frequently one of the most difficult features in reaching a diagnosis of *tetanus is the inability to find on the body* a wound which appears to be a possible portal of injury, as the injury may have epithelized over We treated a boy upon whom no site of injury was noted initially, but finally a small healed abrasion on the leg several weeks old, was found. Beneath the completely epithelized surface there was an area of necrosis, and it was assumed that this had probably been the source of the tetanus growth from which the exotoxin had been liberated

As a rule, the symptoms develop within 1 to 2 weeks following injury, and two general types of findings are encountered. Th first consists of a localized stiffening o twitching of muscles in the region of th wound and may not be recognized as cause by tetanus The second and by far the mor generally recognized variety is that whic is referred to as the descending type. Her the symptoms first begin in the small muscles of the face with stiffening of the masseter muscles, which may progress until i is impossible for the patient to open hi mouth, generally referred to as "lockjaw" Eventually the facial muscles may pull bac at the corners of the mouth to produce th grimace of "risus sardonicus" Later, pharyngeal muscles become involved and it may be difficult for the patient to swallow Deat may occur due to continuation of the proces to involve muscles of respiration, with al most continuous spasm of the diaphragm or other accessory muscles of respiratio which prevents adequate pulmonary venti lation At times the patient may enter a dee coma, lasting for weeks, from which he may

or may not emerge. The exotoxin of the tetanus bacterium is quickly fixed by both specific nervous and other tissues.

Autopsy in fatal tetanus cases may reveal remarkably little. Patients who have had the disease over a period of weeks show considerable wasting of the musculature, as would occur with any other type of starvation.

TREATMENT OF TETANUS. *Serotherapy.* If the patient has not had active immunization with toxoid, from 1500 to 3000 U S P. units of tetanus antitoxin should be given. If symptoms of tetanus should develop 50,000 U.S.P. units should be given at once intravenously, with 10,000 units injected into the muscles in the neighborhood of the wound and 10,000 units intrathecally. This or a similar dosage is then repeated daily until the symptoms have largely subsided.

As soon as serotherapy has been initiated, the wound or any possible site of infection is thoroughly explored and all necrotic material excised. While this may liberate additional amounts of tetanus exotoxin into the blood stream for the moment (and it can), at the same time it diminishes the further production of exotoxin. The patient is placed in a quiet room and adequate amounts of sedation are given. Tracheotomy is often required to permit adequate ventilation of the lungs, and large doses of penicillin are usually given, though its value is questionable. Cortisone has of course been tried here too but has not been efficacious; nor has the use of curare proved to be of significant benefit in maintaining respiration by diminishing muscle spasm. The Drinker respirator may be of much help. A tube is introduced for feeding purposes.

Prognosis It has often been our impression that the prognosis of the individual case of tetanus had been established even before therapy was begun and that it did not make a great deal of difference what was done. Even so such an impression should in no way impede the most vigorous efforts at therapy. One is well advised to be very cautious in offering a prognosis t family, since patients who appear to b ing well may eventually die several v later, whereas others may improve wh was not believed that they would live

Active immunization. By all odds most successful method of treating tet prophylactically is to immunize with to The administration of toxoid has, how no value after the injury has occurred induce active immunity with tetanus to is a slow process that requires week months, and three injections are req to produce optimal immunity. If the pa has received less than two injections of oid prior to an injury, he should cert receive antitoxin. If he has previously a full course of toxoid, a booster dos toxoid is usually sufficient However, i has not received at least one injectio tetanus toxoid previously, antitoxin toxoid should not be administered su taneously. The toxoid will not interfere the antitoxin, but the antitoxin will inte with the toxoid. As for antitoxin, an in tion of 1500 American units confers tit able immunity for from 2 to 3 weeks, 10 units for 6 to 10 weeks and 100,000 f to 11 weeks and possibly longer.

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Chapter 6

The Pathophysiology of Thermal Burns

A severe thermal burn constitutes one of the major unsolved problems in surgical practice. The injury comprises a complex physiologic insult of the greatest magnitude, combined with the special problem of skin loss over a wide area In effect, a burn represents an extensive open wound that cannot readily be closed, because ultimately skin must be obtained from elsewhere on the critically ill patient himself

The more important physiologic aspects of burn trauma and management will be examined under the following headings

A Types of thermal injury
   1 Agents
   2 Magnitude of the burn
      (a) Depth
      (b) Estimation of surface area
   3 Prognosis in burns
B General systemic response
   1 Neuroendocrine reaction
      (a) Adrenocortical secretion
      (b) Thyroid activity
      (c) Adrenal medullary response
      (d) Nitrogen excretion
   2 Other visceral responses
      (a) The cardiovascular system
         (1) Blood pressure
         (2) Blood volume
         (3) Cardiac output
         (4) Capillary permeability
      (b) The lungs
      (c) The gastrointestinal tract
   3 Fluid and electrolyte metabolism
      (a) Stages of the burn
      (b) Fluid shifts between burned and unburned tissues
      (c) Body weight changes during therapy
      (d) Body fluid compartment changes
      (e) Insensible fluid loss
      (f) Plasma chemistry values
      (g) Renal function and urine volume
C Principles of treatment
   1 General supportive measures
   2 The burn wounds
   3 Some complications of an extensive full thickness burn
      (a) "Metabolic decompensation" (early)
      (b) Infection
      (c) Chronic inanition
      (d) Curling's ulcer
      (e) Failure of autografts to "take"
   4. Emotional aspects of the burn

Types of Thermal Injury

Agents

SCALD BURN Most thermal burns are caused by one or more of three types of heat sources. The least serious of these is the scald burn by hot liquids, usually water, in the form of liquid or steam These injuries are usually first and second degree in depth and, while often exquisitely painful grafting is not likely to be required. The prognosis is good except in the very young and the very old, particularly the latter

FLASH BURN A second type of lesion is the flash burn, produced by sudden flames as



Fig 46 A flame burn The right eyeball was enucleated, the wound prepared, and split thickness skin grafts applied

from gasoline explosion Although the radiant thermal intensity may be high, it is brief, and frequently even a shirt and shorts are sufficient to protect these portions of the body This burn is more serious than that resulting from scalds, but it is less serious than that due to actual flames from ignited clothing or other sources The flash burn may require grafting but much of it may not

FLAME BURN A third type of burn, a very serious one, is the flame burn (Fig 46) This usually results in deep, full-thickness (third degree) injury, and much of the wound will require grafting Ninety per cent of the patients who sought aid during the first week following the bombing of Hiroshima and Nagasaki did so because of thermal burns [23]

ELECTRICAL BURN An additional type of burn is the electrical burn, which has certain highly deceptive features The source is, of course, a high tension wire, from which a heavy current passes through the grounded individual who is so unfortunate as to grasp it All too often he cannot turn it loose, since the electrical stimulus maintains the contraction of the muscles employed in the grasp Accordingly, any doubtful source of current should never be grasped, but should be touched with the back of the hand—if it is to be contacted at all, a practice which would appear most unwise to us but one which is not uncommon The electrical burn may be such as absolutely to destroy the hand, exposing the fragments of the partly disintegrated phalanges and metacarpals (Fig 47) Furthermore, the site at which the current leaves the body, where it is grounded, also frequently represents a wound of considerable proportions Perhaps the most distinguishing single feature of the electrical burn, however, is the remarkable extent of the irreversible damage extending from the point of entry This is usually impossible to delineate on admission First the hand is amputated, then the forearm and, not infrequently, finally the arm at the shoulder In other words, the extent of the vascular destruction may be revealed only after a period of days or weeks



Fig 47 An electrical burn of the hand The extent of arterial and other tissue damage following electrical injury is often far more extensive than is at first apparent

Magnitude of the Burn

DEPTH The burn is a three dimensional injury—length, breadth, and *depth* That is, the severity of the burn is a function of its depth and the surface area involved It is important to appreciate that different areas of the burn may vary widely in depth, and that this will be an important factor in treatment and prognosis

The depth of the burn is classically described as follows *First degree* burn is that which is erythematous only, without blister formation or skin loss *Second degree* burn connotes blister or vesicle formation but does not ultimately require grafting *Third degree* or full-thickness burn destroys all layers of the skin and must eventually be grafted if it involves more than a minor

surface area which could be allowed to heal by scar formation It is notoriously difficult to estimate with precision at the time of admission which portions of the injury are deep second degree and which are third degree To excise and graft immediately is to risk excising viable tissue, rendering the over all insult greater than it needed to be, on the other hand, to delay unduly, in order to be certain that no viable tissue is excised, may permit infection and inanition so to debilitate the patient that he can neither tolerate the removal of extensive autografts nor marshal the metabolic requirements for successful takes

Some full thickness injury is always expected following a flame burn In the white patient, third degree injury is probable when the skin is dry and leathery or dead white and cadaveric or deep pink with thrombosed vessels which show through the parchment like skin, or presents broken blisters with a roseate pink beneath, or, of course, if it is charred. However, the fact that the surface is still covered by intact blisters does not ensure that third degree injury does not exist time will tell

In the Negro many of these same findings are helpful but the color changes in the skin are usually far less pronounced. In deep second degree burn the skin pigment may be lost, and thereafter the healed skin is much lighter in color than surrounding normal skin similar to changes at the donor sites from which skin grafts were taken.

ESTIMATION OF SURFACE AREA. The body surface area involved is conveniently estimated for therapeutic if not precise scientific purposes using the familiar 'rule of nines (Fig 48) It is highly desirable to record on the patient's chart the admission estimate of the extent of first and second degree burn as compared with a separate estimate of third degree burn. At times one may be able to discern only that the full thickness injury involves the skin, whereas underlying muscles, tendon, fascia and occasionally even bone may be involved.

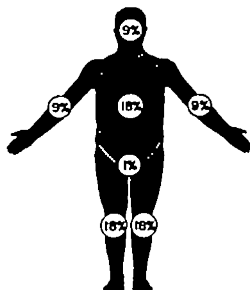


Fig 48 The rule of nines Satisfactory approximations of the surface area burned can be achieved using this diagram

Prognosis in Burns

Of all traumatic injuries, burns afford an opportunity to state with considerable accuracy at the outset the probable eventual result of the case This is but an indirect way of stating that the extent of the *area and depth* of the initial injury and the *age of the patient* are the primary factors which determine prognosis, regardless of the treatment used To be sure deaths due to early burn shock have declined as transfusional therapy has improved but many of these patients go on to die from other causes during subsequent weeks Therefore, while the length of time burned patients live has been increased, the mortality resulting from thermal injury has not been materially reduced [21]

The mortality from the Burn Unit of Birmingham Accident Hospital (England) was analyzed by Bull and Squire[4] on the basis of 794 patients who required inpatient hospital treatment from 1945 through 1947 Their findings are presented in Figures 49 and 50 In the first the mortality was plotted against the per cent of surface area burned It is seen that whereas virtually no mortality occurred following burns of less than 10 per cent, full thickness injuries of greater than 60 per cent were associated with almost 100 per cent mortality In Figure 50 the per cent

area burned was plotted against the age in years, with mortality shown on each of the five curves Note that what would constitute a minor burn in the younger individual results in an appreciable mortality in the patient over 70 A 70 per cent burn in an individual of 10 years is associated with a 90 per cent mortality; but a 20 per cent bu in an individual of 70 years may produce similar mortality

The prognosis given to relatives followi any burn in an elderly individual should guarded In a man of 20, a 50 per cent fu thickness burn would carry a 50 per ce chance of a fatal outcome, despite the m energetic management Yet, in the indiv. ual case uncontrollable complications m subsequently offset the initial advantage less area burned

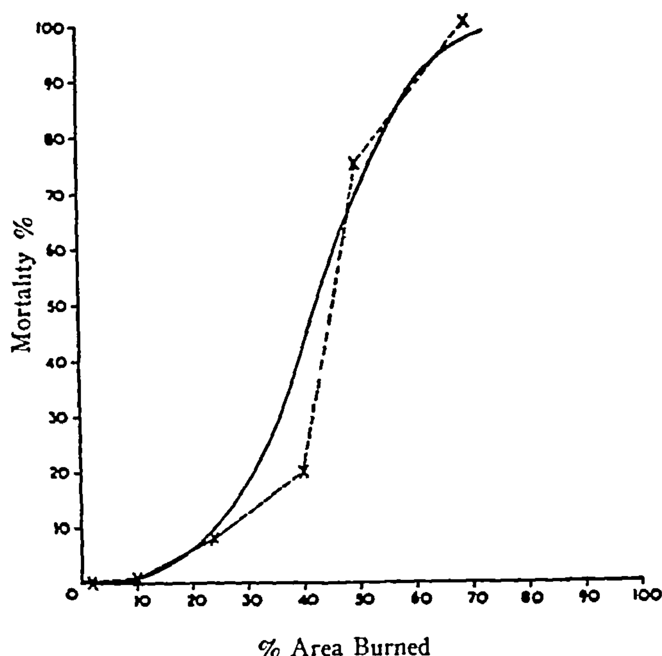


Fig 49 Relationship between extent of burn and mortality The age of the patient and the extent of the burn are the basic factors in prognosis (From BULL, J P, AND SQUIRE, J R A study of mortality in a burns unit Ann Surg, **130:** 160, 1949)

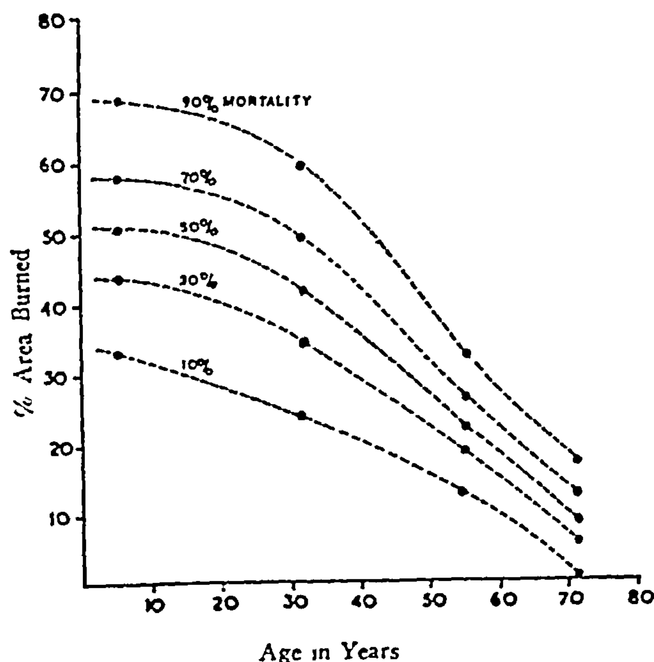


Fig 50 Relationships between extent of burn, age, and mortality (From BULL, J P, AND SQUIRE, J R A study of mortality in a burns unit Ann Surg, **130:** 160, 1949)

General Systemic Response

Neuroendocrine Reaction[10]

ADRENOCORTICAL SECRETION The metabo response to trauma was described in Chap 1 and qualitatively this response to burns not materially different Quantitative however, the reaction to extensive full-thic ness injury exceeds that of almost any otl stimulus studied in our laboratory In Figu 51 are shown the urinary excretion of *cor coids* and *17-ketosteroids* and the *total e sinophil counts* in a patient who died the thirty-ninth day with septicemia (C tain water and electrolyte measurements this patient are presented in Figure 5 There was the usual vigorous increase adrenocortical secretion, resulting in markedly elevated excretion of corticoi this persisted virtually to the time of dea but during the last 24 hours oliguria w present The excretion of 17-ketostero was initially somewhat elevated, but duri the ensuing weeks of infection and inaniti the excretion of these products of androge precursors gradually declined to a low lev this is the usual finding in a seriously d pleting illness, but the level again rises normal during convalescence, perhaps a counting for the return in sexual interest males at this time In this respect, therefo the level of excretion of 17-ketosteroids a fords an index of the functional reserves the individual and of the progress of co valescence

The *total eosinophil count* in this patie

was at zero on admission and remained essentially at zero throughout life, indicating severe and continued stress In general, it was found that when the total eosinophil count remained at zero level the injury was a serious one and the prognosis uncertain, in contrast, when the count rose promptly from zero after the first 48 to 72 hours the injury was likely to be less extensive and hence the prognosis more favorable.

Studies of plasma corticoid levels following burns have reflected the alterations in adrenocortical activity previously described on the basis of urinary excretion studies More than 85 per cent of the corticoid secretion by the adrenal cortex consists of hydrocortisone.

The derangements in carbohydrate metabolism observed following burns and other trauma are probably the result of increased adrenocortical secretion, with increased insulin resistance.

THYROID ACTIVITY Thyroid function before and following experimental burns was studied by Wase and Repplinger,[27] who found evidence that thyroid uptake of radioiodine was reduced during the first 4 hours following burning but thereafter was increased Cope and his associates[8] on the other hand, could find no evidence that thyroid activity was significantly altered following thermal injury Wase, Eichel, and Repplinger[26] also approached this question by studying nitrogen excretion They found that the postburn nitrogen excretion of euthyroid rats approached that of hyperthyroid rats while the nitrogen excretion of hypothyroid animals was virtually unchanged following the injury

However one should look upon the question of whether or not thyroid activity is altered by trauma as being still unsettled, our personal suspicion is that thyroid activity is increased

ADRENAL MEDULLARY RESPONSE. The means for studying blood levels of epinephrine and norepinephrine have only recently been practicable for clinical investigations. Therefore relatively few measurements

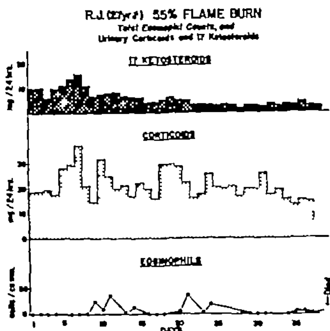


Fig 51 Adrenocortical response to a flame burn The gradually decreasing level of 17-ketosteroid secretion reflected depletion of the patient The elevated corticoid excretion continued to death The total eosinophil count rarely rose above zero throughout life (From WILSON H., LOVELACE, J R., AND HARDY J D Adrenocortical response to extensive burns in man Ann Surg 141: 175 1955)

have been made We have observed in a number of burned individuals an hypertensive response which persisted for a number of days[17] It is quite possible that this represented an increased sympathomimetic discharge

NITROGEN EXCRETION As in other trauma, extensive burns are associated with a massive nitrogen loss (as well as fat), which can in part be offset by vigorous intravenous alimentation with fortified protein hydrolysate preparations and intravenous fat.[2] We found that the amino acid composition of this nitrogen wastage in the urine was not qualitatively different from that in other forms of trauma[9]

Other Visceral Responses

THE CARDIOVASCULAR SYSTEM *Blood pressure* The blood pressure is the most reliable single guide as to the adequacy of fluid therapy in the burned individual (Fig. 52) Following the injury the circulating blood volume begins to decline, unless therapy is begun. If this reduction in circulating blood

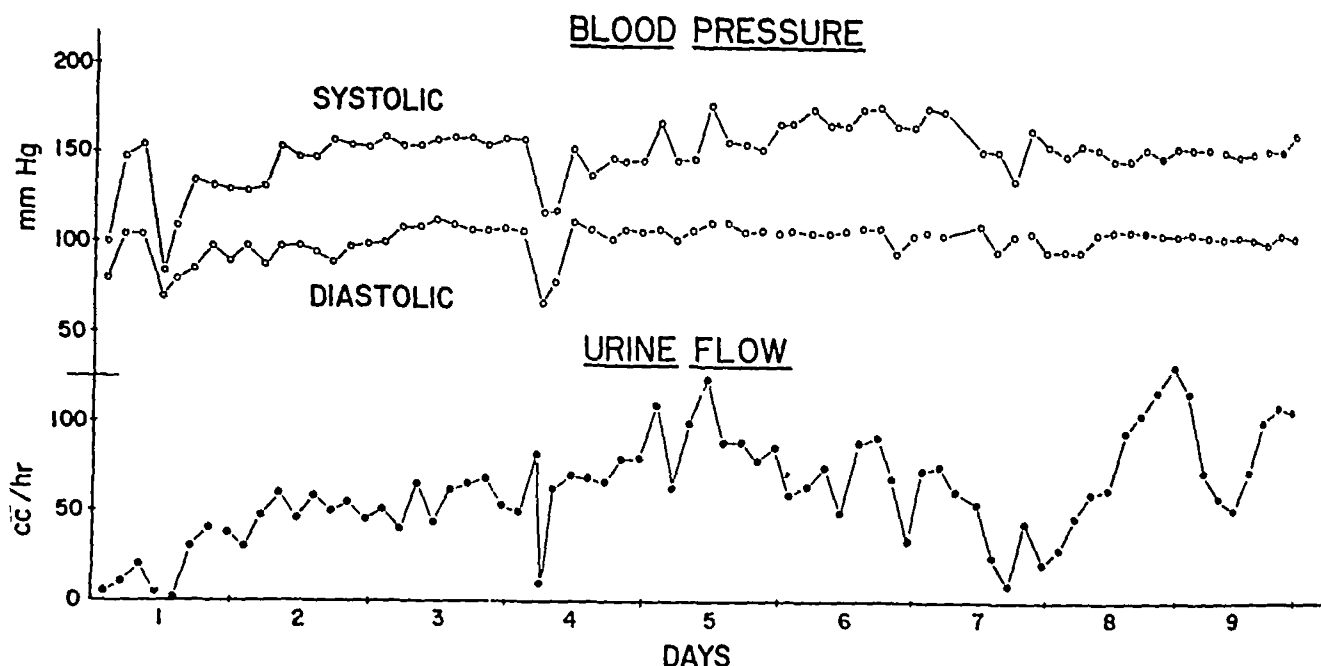


Fig 52 Relationship between blood pressure and rate of urine flow Note that twice on the first day and once on the fourth day the urine output promptly fell when the systolic blood pressure in this normally hypertensive subject fell to around 100 mm Hg (HARDY, J D Unpublished observations)

volume is great enough, the blood pressure falls It has been found that when the patient is given volumes of replacement therapy sufficient to restore and maintain blood volume, he almost invariably gains weight due to fluid retention Whereas shock formerly was common in burn patients, the volumes of fluid given in therapy are now usually effective in preventing significant hypotension in most patients in whom the therapy is begun promptly after the injury

In Figure 52 the urine flow is plotted against blood pressures for 6-hour periods in an extensively burned subject To avoid any possibility of excessive fluid administration in this obese elderly individual, the intravenous colloid, saline, and glucose solutions were ordered only as needed to maintain an adequate blood pressure level in this normally hypertensive subject That the fluids given were only barely sufficient was reflected in the fact that once during the first 24 hours the blood pressure fell to a shock level, at which time urine flow declined somewhat from the already minimal level Actually, the fluid required to maintain a satisfactory blood pressure proved to be almost equivalent to that which had been calculated to be necessary on the basis of Evans' formula,[11] our usual rule of thumb; of course, it was by means of noting the volumes of colloid and other solutions required to effect satisfactory blood pressure levels and rates of urine flow that Evans developed his formula

It was of interest that the patient exhibited a second hypotensive period on the fourth day, which again responded to intravenous therapy Nevertheless, we have observed such episodes even as late as the tenth postburn day The important point is that the patient may die of remediable shock at any time for a considerable period after the injury Since oliguria may be due to a variety of factors, the therapy should be adjusted on the basis of further clinical data including blood pressure

Blood volume The blood volume rapidly declines in the presence of an extensive burn, as remarked above This is due to loss of extracellular fluid into the burn areas, to an increased capillary permeability for the

plasma proteins, and to a destruction of red cells Realization of the magnitude of this reduction in blood volume led to the more effective treatment of burn shock, which has been perhaps the most notable advance in burn therapy during the past 20 years

Cardiac output Immediately following the burn—during the period of hemoconcentration, oligemia, and perhaps shock—the cardiac output is often subnormal However, this responds promptly to effective fluid therapy, and thereafter the level of cardiac output rises not only to normal levels but may even exceed them (Fig 53) The re-establishment of a normal level of cardiac output usually reflects fluid therapy that is adequate, at least for the moment In patients who survive, the cardiac output gradually subsides from the markedly elevated levels recorded during the intermediate (or subacute, or "toxemic) period to essentially normal levels

We performed multiple serial measurements of cardiac output in 11 extensively burned subjects.[18] In only 4 was shock present at the time of the initial cardiac output measurement, in these the values ranged from 2 to 4.6 L. per minute (average normal 5 L or more)

Capillary permeability Netsky and Leiter[22] showed in 1943 that capillary permeability was increased not only in the burned area but in the nonburned areas as well This results in an abnormal rate of loss of plasma proteins from the intravascular space Later, citing Drinker's work, Cope and his associates[6, 7, 10] pointed out that a definite amount of protein normally passes across capillary membranes leaving and re-entering the plasma The lymph protein and therefore presumably that of the interstitial fluid varies from less than 1 per cent in the superficial tissues of an extremity to as much as 5 per cent in the liver The protein content of bleb fluid has been variously recorded at 60 to 80 per cent of that in plasma the albumin globulin (A G) ratio in bleb fluid is much increased over that in plasma due to the greater capillary

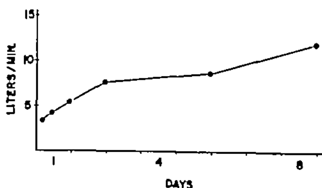


Fig 53 During the period of hypotension the initial cardiac output value (blue dye method) was 3.5 L. per minute Thereafter the cardiac output rose progressively This rise was characteristic of all patients studied (15) it gradually subsided in patients who did not die (HARDY J D Unpublished data)

permeability for the small albumin molecule than for the larger globulin

THE LUNGS The participation of pulmonary components in the general reaction to injury was mentioned previously This aspect of the stress response has been little studied but, unless the lungs are directly involved in the burn injury through the inhalation of gases, a deleterious effect of the burn on lung function is not especially apparent. To be sure pulmonary difficulties of some degree arise in almost any patient immobilized in bed with infected wounds and treated with large volumes of salt-containing fluids Tracheotomy is often of material assistance and it may be a lifesaving procedure if the burns have involved the face and the tracheobronchial tree

THE GASTROINTESTINAL TRACT One of the common requests of the patient admitted in burn shock is for water Even so, the gastrointestinal tract of the extensively burned subject is by no means normal in function food is poorly tolerated because of abdominal distention and intestinal atony that are often associated with nausea and vomiting but less often with diarrhea Despite the desirability of using the oral route for fluid administration where possible the more seriously burned subjects who need

fluids most, are least able to tolerate oral intake Therefore, we use the intravenous route almost exclusively in severely burned subjects

Fluid and Electrolyte Metabolism

STAGES OF THE BURN It is common practice, as well as convenient, to divide the natural history of the burn into the following stages shock, toxemia, grafting and repair, and late convalescence However, the burn picture, as we know it from a physiologic standpoint, continues to be modified in the light of unfolding knowledge, and we now prefer a classification of the physiologic aspects of the burn injury that is somewhat different from the classical one above Our preference is as follows.

1 *Stage of shock (first 48 to 72 hours).* Maximal fluid therapy

2 *Stage of sodium and water retention (from first to seventh day)* Cut back fluid therapy after shock stage passed Treat acidosis, if present

3 *Stage of sodium and water mobilization and diuresis (from the fifth or seventh to the twelfth to fourteenth day)* Careful attention to blood replacement and to plasma electrolytes, particularly to acid-base balance

4 *Stage of anemia and malnutrition and, often, infection (from fifth day onward)* Transfuse and feed

5 *Grafting completed and danger abated*

The *stage of toxemia* in burns appears more and more to derive its principal distinguishing characteristic—fever—from wound infection and, often, septicemia In fact, septicemia is one of the more common causes of death in burns The stages of shock, fluid retention, and fluid mobilization are well illustrated in Figures 53 and 55

FLUID SHIFTS BETWEEN BURNED AND UNBURNED TISSUES Much of the progress in our knowledge of burns achieved over the past three decades has had to do with a more precise understanding of the nature and magnitude of the relatively enormous fluid shifts that occur between the burned and the unburned tissues One of the early and conclusive demonstrations that fluid a[illegible] mulated beneath the burn wound was of Blalock[3] In a delightfully direct ex[illegible] ment, he burned one side of an animal, mitted time for edema fluid to accumu[illegible] and then separated the two halves of body sagittally from nose to tail the bu[illegible] half of the carcass was shown to weigh siderably more than the unburned half

Thus, following a burn of, say, an tremity, the part swells due to the accu[illegible] lation of wound edema fluid This local of fluid and electrolytes into the wound neighboring tissues proceeds most rap[illegible] during the first 8 hours following the b[illegible] ing and reaches a maximum in 48 h[illegible] after which the swelling gradually [illegible] sides[5, 7, 20, 24]

Fox and Baer[12] devoted special atten[illegible] to the shifts of water, potassium, and sod[illegible] between the burned and the unburned sues In brief, they reported that the sod[illegible] content of the injured tissues increa[illegible] whereas the potassium content decreas[illegible] in contrast, the tissues in the "normal" a[illegible] of the body of the experimental animal c[illegible] tained less than the normal amount of dium but increased amounts of potassi[illegible] It was deduced from such findings that potassium lost from the injured cells [illegible] taken up by the uninjured cells elsewh[illegible] in the body, that the loss of sodium in[illegible] cess of water into the burned area produ[illegible] hypotonicity of the extracellular fluid, [illegible] that this permitted water to move into [illegible] cells, even further reducing the extracellu[illegible] volume and, with it, the plasma volu[illegible] They concluded that treatment with amount of isotonic sodium solution appr[illegible] imating one-half the extracellular space [illegible] stored extracellular volume On this ba[illegible] the successful treatment of shock in anim[illegible] (Rosenthal) with isotonic saline was co[illegible] sidered to have been explained[27] Fox [illegible] timated that as much as almost one-h[illegible] the extracellular sodium could be lost in the burn wound edema or into injured cel[illegible] resulting in a loss of extracellular fluid

similar magnitude, moreover, these conclusions were supported by the fact that the infusion of a volume of saline solution equivalent to approximately one half the normal volume of the extracellular fluid might suffice to preserve blood volume, blood pressure, and urine output in experimental burns involving no more than 20 to 25 per cent of the body surface area.

BODY WEIGHT CHANGES DURING THERAPY The extensively burned patient treated adequately to prevent shock almost invariably gains weight during the first 3 days when fluid intake is maximal but urine volume is diminished (Figs 54 and 57) This gain occurs despite fluid losses through the skin and burn wounds which vary considerably from patient to patient and in the same patient from day to day These losses can amount to several liters

The weight curve begins to decline on from the fourth to the seventh postburn day, and this process is usually complete by the end of the thirteenth day this is concomitant with a decrease in fluid intake, an increase in urine volume, a negative nitrogen balance (indicating tissue catabolism) and, at times, an apparent increase in the insensible fluid loss" from the normal skin, the burn wounds, and the lungs.

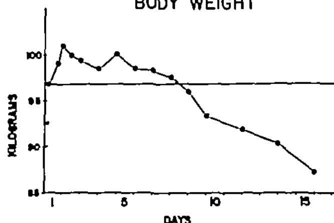


Fig 54 The initial rise in the body weight curve was due to fluid retention The persistent decline following excretion of the retained fluid was due to the ravages of fever infection, and starvation

Since the volume of fluid infused in our studies increased with the per cent surface area burned (up to 50 per cent, which was used as a maximum burn in estimating fluid requirements) it was not surprising that

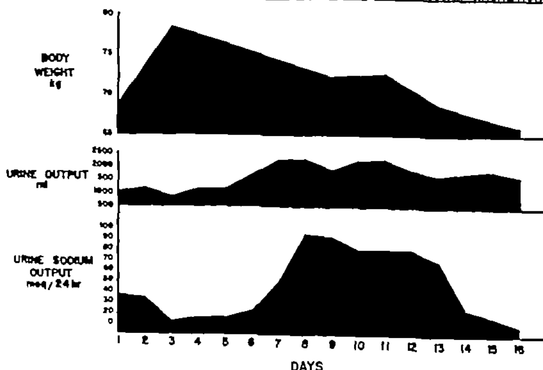


Fig 55 The water and sodium retained initially were excreted beginning on the fifth post burn day (From HARDY J D NEELY W A WILSON F C., JR MILNOR, E P AND WILSON H Fluid kinetics following thermal burns in man. Surgery 34: 457 1953)

there was a direct correlation between the extent of the burn and the degree of weight gain during therapy[13] The maximum weight gain recorded was 22 + lb or 10 kg (Fig 55) Incidentally, this patient had by the end of the second week lost all the weight gained and by the end of the fourth week had lost 25 lb (11 kg) of tissue, a body weight fluctuation of almost 50 lb over a 4-week period

BODY FLUID COMPARTMENT CHANGES To determine the compartmental distribution of the relatively large volumes of fluid administered to burn patients, we determined total body water values in seven patients on admission and over the first several days of treatment[14] Representative subjects are shown in Figures 56 and 57 Both body weight and thiocyanate ("extracellular") space increased in all subjects and, in general, the increase in thiocyanate space usually exceeded the increase in weight Most of the fluid given in therapy would appear to remain extracellular

INSENSIBLE FLUID LOSS The "insensible fluid loss"—consisting of all losses from wounds, normal skin and lungs—was studied by means of weighing burn patients twice daily and carefully recording all intake and output[16] As previous workers had found, the volume of insensible loss tended to bear a direct relation to the magnitude of the

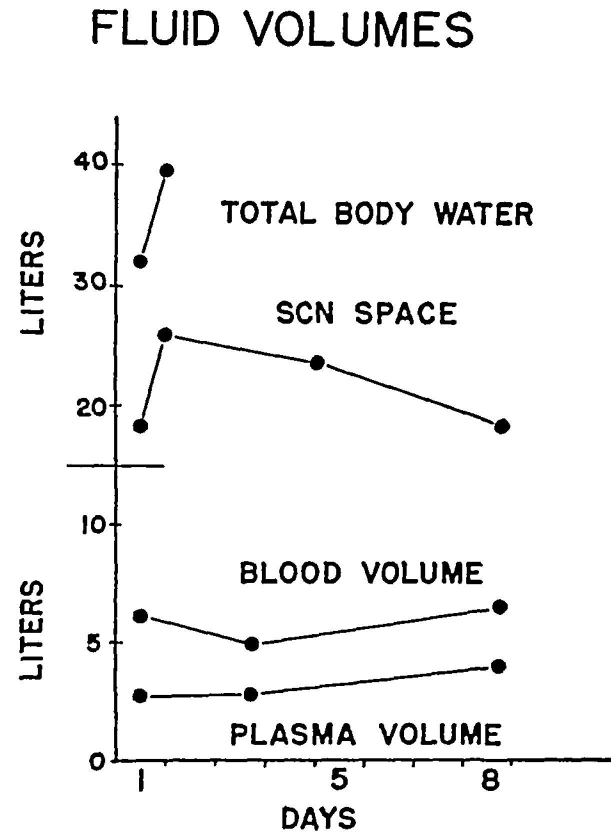


Fig 56 The increase in total body water (and body weight, see Fig 54) was due largely to an increase in the extracellular volume Note the decline in red cell mass on the third postburn day (HARDY, J D Unpublished data)

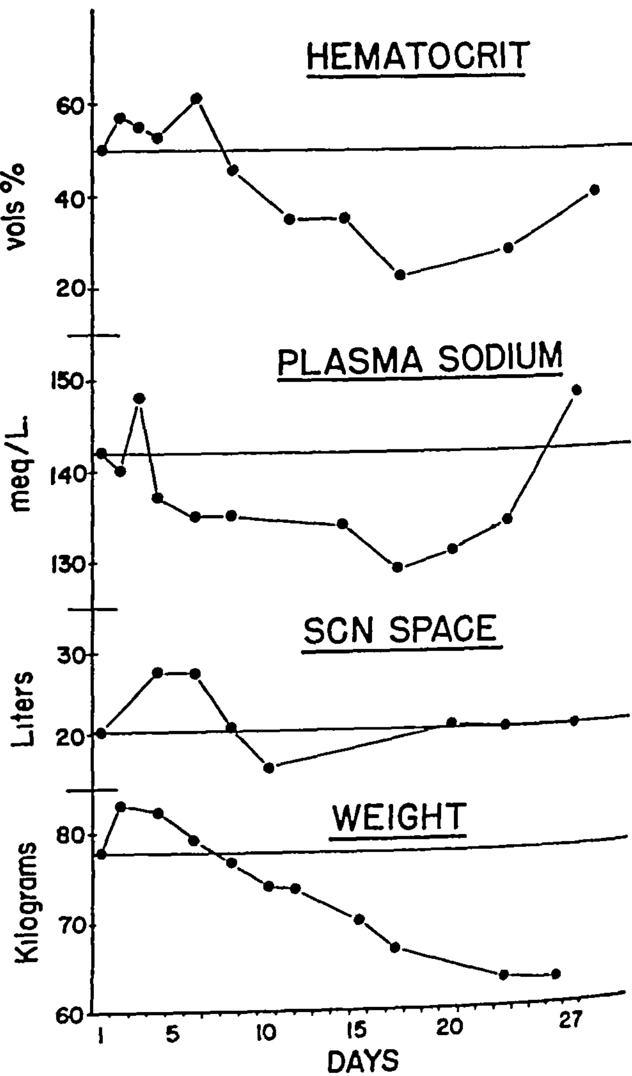


Fig 57 Relationships between hematocrit, plasma sodium level, thiocyanate space, and body weight The increase in body weight was due to fluid retained in the extracellular space The fact that the plasma sodium level declined further after the thiocyanate space had returned to normal would appear to weigh against a simple dilution effect as the only cause of the hyponatremia (HARDY, J D Unpublished data)

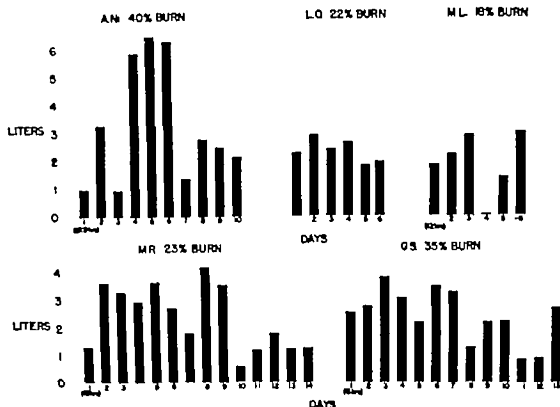


Fig 58 Insensible loss varied widely from patient to patient and in the same patient from day to day (From HARDY J D WILSON F C., JR AND NEELY W A Thermal burns in man VII Insensible and wound fluid losses during early therapy Surgery 38: 692 1955)

injury Moreover, certain patients had relatively little insensible loss for the first few days, followed by relatively massive losses later (almost 5 L in one patient on each of two consecutive days) Perhaps the most surprising finding of all though, was the remarkable variation in insensible loss in the same patient on consecutive days (A. Ni Fig. 58)

Unquestionably the insensible loss may constitute a major factor in influencing fluid requirements in some burn patients

PLASMA CHEMISTRY VALUES Cumulative data obtained from a number of patients have been presented graphically in Figure 59 In general there was a decline in the plasma sodium level, no consistent change in the chloride level, a rise in the nonprotein nitrogen (NPN) level a subnormal plasma carbon dioxide combining power, and a gradual decline in the plasma potassium values The urine volume increased progressively from the beginning of the treatment through the ninth day

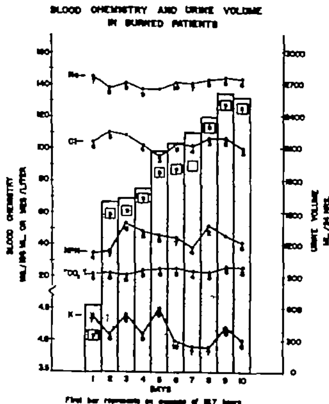


Fig 59 Averages obscure significant variations Serious acidosis occurred in several patients (HARDY J D., AND BRADLEY E E Unpublished data)

While average values indicate probabilities, they also obscure highly significant exceptions from the general trend Perhaps the most striking exceptions exhibited by individual patients were quite low plasma sodium and carbon dioxide combining power values Furthermore, acidosis was treated more frequently in this group of patients than might appear to have been necessary, should the averaged values be taken completely at face value One patient developed marked hypernatremia and hyperchloremia (Fig 60)

RENAL FUNCTION AND URINE VOLUME Haynes and his associates[18] studied renal function in 16 severely burned patients and found a relatively constant pattern of response; it was characterized by an increase in glomerular filtration rate, a normal effective renal plasma flow, and an increased filtration fraction This pattern was noted within the second day postburn, and the filtration rate and filtration fraction declined to reach and maintain normal values at 2½ to 3 weeks after injury Tubular function, as measured by the maximal tubular excretory capacity, was within normal limits after injury in a group of severely burned but adequately treated patients

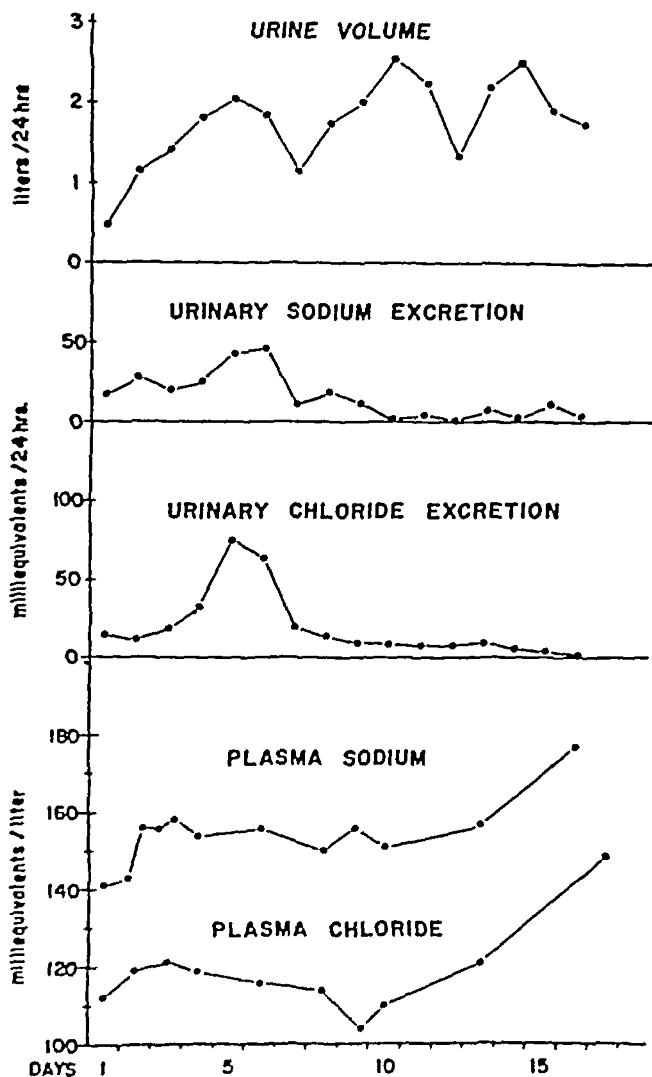


Fig 60 Hyperchloremia and hypernatremia with good urine output Note that there was virtually no sodium or chloride in the urine (Hardy, J D Unpublished data)

In 26 patients studied by us whose burns exceeded 15 per cent (range, 15 to 85) of body surface area, only one subject (a 82-year-old female) appeared to have di primarily from renal failure *per se* Th was somewhat surprising, since it had bee anticipated that the incidence of acute ren shutdown would be greater

In the cardiac output studies, while a lo cardiac output was usually associated wit a low urinary output, the reverse was nc necessarily true, for there were causes c oliguria in addition to that which resulte from a diminished cardiac output Ther was, of course, a close correlation betwee blood pressure and urinary output, in tha hypotension almost invariably resulted i oliguria.

Principles of Treatment

General Supportive Measures

FLUIDS USED IN THERAPY VOLUME AND COMPOSITION. Since most of the fluid loss into the burned areas occurs during the *first 48* hours, a major portion of the *fluid* given in therapy must be given during the first 24 hours following the injury, if shock is to be effectively combatted Actually, we give approximately one-half the first day's requirements during the first 6 hours after the burning, the rest over the next 18 hours Moreover, it is particularly important to give a substantial portion of the estimated colloid solution requirement early

While one can by constant attention tr at

the burn patient successfully by following multiple blood pressure measurements—and these measurements are taken frequently in any case—it has proved practicable and effective to estimate the volume of colloid (blood, plasma, plasma expander), saline, and glucose solutions required for the first 24 to 48 hours on the basis of some convention or "formula" We use that described by Evans[10, 11] and have found it most helpful if adjusted to meet the varying requirements of the individual case For example, if the patient is quite old the volume of fluid given is kept on the low side rather than to risk excessive fluid therapy that might precipitate circulatory failure Furthermore, if the patient is markedly obese the fluid requirements are estimated on the basis of the estimated ideal weight in conjunction with the per cent area burned, for fat contains little water, and to "calculate" fluid requirements on an exact weight basis in the very obese could result in serious over treatment.

The fluid required in treatment is as follows [11]

First 24 hours

Blood plasma, or plasma expander multiply per cent body surface area burned by body weight in kilograms (e g a 40 per cent burn × 70 kg)	2800 cc
Isotonic saline (or 2 parts isotonic saline and 1 part M/6 sodium bicarbonate) Again per cent burn × 70 kg	2800 cc
Glucose solution (5 or 10 per cent)	2000 cc
Total volume	7600 cc

Second 24 hours

Take one half the volume of each solution used during the first 24 hours maintaining the 2000-cc glucose solution if desired

Blood plasma or plasma expander	1400 cc
Saline solution	1400 cc
Glucose solution	1000 cc

Again these volumes frequently need to be modified somewhat in the individual case However, the formula was derived from actual requirements recorded from a large clinical and experimental experience. It is a very convenient guide during the first 2 days when fluid requirements might otherwise be continuously underestimated and episodes of shock result. After the first 2 days the fluid therapy must be planned on the basis of the effectiveness of previous therapy, judged from the total clinical evaluation of the patient After 48 hours the hazard of shock rapidly diminishes

In evaluating the clinical situation, the arterial blood pressure, the rate of urine flow, and the appearance and orientation of the patient are the most useful guides to progress The hematocrit is usually elevated due to hemoconcentration but, while we have commonly used plasma expander to maintain the level below 60, there has been no conclusive evidence that the elevated hematocrit level is deleterious

Anemia is a prominent feature of the extensive burn James and his associates[19] found this due not only to red cell destruction by the injury but also to a diminished rate of hemoglobin formation Repeated whole blood transfusion is necessary

SEDATION IN BURNS The superficial burn may be far more painful than the deep, full thickness injury, in that the cutaneous nerve endings often have been destroyed in the latter Therefore, morphine should not be indiscriminately administered, if the patient has no pain but does need sedation a barbiturate is preferable in that it produces less respiratory depression than opiates

MANAGEMENT OF ACIDOSIS The common acid base derangement in burns is an acidosis that may appear quite early For instance one severely burned subject exhibited a plasma carbon dioxide combining power level of 16 mEq on admission 2 hours after burning. Intravenous or oral sodium bicarbonate solution is a satisfactory material for the management of this acidosis,

given as required to maintain the "CO_2" above 20 mEq/L of plasma We do not attempt to correct the "acidosis" entirely, the depressed "CO_2" may be in part the result of a renal *retention of organic and fixed acids* (Fig 19) In many cases an actual pH change may not exist For this reason, the character of the respirations should be used as an additional guide to alkali requirements

The Burn Wounds[1]

Whereas it is the wounds—their extent, their depth, whether infection develops (it usually does), whether grafting is promptly successful—that ultimately determine survival of the patient in most instances, known physiologic considerations are not paramount issues in early local management After prolonged observation, we are not convinced that the open or exposure method has a significant advantage over the closed method—and the open method is usually abandoned as grafting of the wounds is begun However, there is often much convenience in using the open method initially

When the open method is to be used, we perform virtually no debridement, but simply place the patient in bed under a cradle, using "sterile" sheets so that the organisms that he brings will not be unduly increased by others Even with the closed method debridement is minimal, for to open blisters is to lose plasma and to invite more infection *Adequate tetanus prophylaxis on admission is mandatory*

The early physiologic problems have to do with fluid and plasma losses from and into the burned areas These considerations continue into the subacute and chronic periods, with blood loss also important Moreover, the loss of a large area of functional skin renders the individual exceptionally susceptible to variations in ambient temperature Exposure of the entire raw surface in an air-conditioned operating room under anesthesia for several hours may result in a decline in rectal temperature to levels of 95° F or lower Conversely, in some cases the application of bulky dressings over much of the body surface, when room temperature during the summer may be ranging to from 95 to 100° F each afternoon, may occasion serious difficulties in the dissipation of body heat

Removal of the slough in third degree burns presents difficulties that have never been satisfactorily solved To excise compromised tissue early is to risk removing viable tissue, since appearance is often deceiving on admission Furthermore, the areas involved are often too extensive to be excised at one time and grafted Yet careful attention to the wounds permits earlier closure This desideratum of removing slough to diminish infection and to prepare for grafting led to the investigation of various enzyme preparations for this purpose to spare the patient the trauma of actual surgical excision These efforts, while not yet conspicuously successful, are still under investigation

Some Complications of An Extensive Full Thickness Burn

The patient with a severe burn may, of course, have any of the familiar complications of a serious and prolonged illness, such as coronary occlusion, pulmonary embolism, hemiplegia, and others Nevertheless, there are certain complications which account for a majority of the deaths in burn patients and these should be mentioned

"METABOLIC DECOMPENSATION" (EARLY) The injury, such as an 85 per cent flame burn, may constitute, even with essential therapy, more of an onslaught than the patient can withstand, death may occur during the first few days, though not from shock *per se*

INFECTION Surely infection beneath the burned surfaces, often resulting in septicemia proved by repeatedly positive blood cultures, is one of the most lethal of the complications of burns The organisms isolated from the blood stream are frequently refractory to all available antibiotics, a Proteus bacterium being a common finding All too often the wounds are heavily infected,

with purulent material beneath the crusts, before debridement can be achieved to provide a healthy granulating surface for grafting.

CHRONIC INANITION In Figure 54 it may be seen that, even after the fluid retained during early therapy has been excreted, the weight curve continues inexorably downward in the severely burned patient, reflecting not only a continued catabolism of fat and lean tissue but also the failure to achieve satisfactory food intake in these subjects Again, food given by the gastrointestinal route often results in vomiting, distention, or diarrhea in these subjects, whereas up to the present intravenous alimentation has been quite inadequate in these patients whose requirements may be several times the normal level With the advent of safer intravenous fat preparations, however, it is hoped that adequate nutrition can be more readily achieved The preparations presently available require further study

CURLING'S ULCER. This is a "stress ulcer" (probably a variant of Cushing's ulcer caused by the stimulus of intracranial injury) which may be related to increased adrenocortical activity It usually involves the stomach or duodenum and is manifested by hematemesis, melena, and further anemia. This lesion may result in death but conservative therapy is usually employed to avoid gastric resection in an already critically ill subject.

FAILURE OF AUTOGRAFTS TO "TAKE." Some patients exhibit a distressing failure to accept split-thickness grafts of their own skin as coverage for the burn wounds At times this failure can be attributed to "anemia" or malnutrition" or " inadequate preparation of the recipient surface' or to "infection" However not always can these possible explanations be invoked, and there is a genuine need for further study of the physiologic requirements involved in successful autografting in addition to the large volume of effort being devoted to finding a means of achieving successful skin homografting

Emotional Aspects of the Burn

This discussion of burn management would be incomplete without mention of the tremendous psychiatric problems that are involved. On admission, the physician often examines a husky person in the prime of life who is vaguely aware that he has suffered a calamity but who is bravely prepared to meet it. Unfortunately, as the weeks of wasting pass and the pain and worry occasioned by changing of the dressings and the multiple anesthetics for skin grafting take their toll, the individual may lose his ability to cope with even minor problems He is often reduced to a whining, shrinking creature, in whom the original person is hardly discernible.

Different, but also very real, are the emotional problems which the physician himself experiences in the treatment of these patients It is not easy to care for the extensively burned subject, for the prognosis is usually questionable and the patient is rarely cheerful as time lengthens Moreover, it is extremely frustrating to treat a patient for perhaps a year or more, and then to have him die abruptly from causes which one believes should have been (or one day will be) preventable by different therapy

The following two patients are illustrative Two girls one 6 years old and the other 11, had been badly burned, the younger almost 2 years before and the older several months before The parents of the younger child had long since stopped coming in regularly to see her, but she had developed a great fondness for the older child. Skin grafting had been repeatedly (but with only partial success) attempted on both, though it had been attempted far more often on the younger girl, she had maintained a courageous attitude over all the months of innumerable transfusions, tube feedings, grafting procedures and febrile periods during which it appeared she would surely die At Christmas (1956) it was decided to allow both girls to go home by ambulance for a few days as a morale-building gesture, though it proved to be an ill fated one

Shortly upon their return the older girl suddenly developed an overwhelming pneumonia and died within hours Distressing as this was, the *younger child immediately turned toward the wall, refused all food or to cooperate in any way (a mode of behavior previously alien to her), and exhibited a steadily declining weight curve and general condition* A few days later she began to vomit blood, and within several more days had died Autopsy revealed more than one gastric ulcer

Who can say that this child's death was not in significant measure a result of the loss of the only person with whom she had established a supportive relationship?

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Chapter 7

Some Physiologic Considerations in Cancer—Etiology, Spread, aud Control

Etiology of Cancer

Though the basic cellular change in carcinogenesis is obscure, much is known with respect to means by which cancer can be produced

Hereditary Factors

TUMORS IN IDENTICAL TWINS In cancer, as with almost every other disease, the influence of heredity has always been of interest Particular impetus was given to such studies in the cancer field by Maud Slye's investigations of the incidence and inheritability of spontaneous tumors in mice [72] In brief, she demonstrated that by careful inbreeding one could develop strains which were relatively resistant to the development of spontaneous tumors and other strains in which almost the entire group would develop spontaneous tumors These studies stimulated great interest in tumors in "cancer families" and in twins In an exhaustive study of tumors in twins made by MacFarland and Meade[45] in 1932, the frequent occurrence of "similar, simultaneous, and symmetrical" tumors in identical twins was reported, in contrast, similar tumors in nonidentical twins were rare In 1940, Macklin[46] reviewed a series of 62 pairs of identical twins, in which both were affected by tumor in 38 instances (61.3 per cent), with similar tumors occurring in 36 of the 38 pairs of the twins (94 7 per cent) The difference in age at the time of onset of symptoms in the pairs of twins averaged 1½ years In contrast, in 43 pairs of nonidentical twins both were affected by tumor in 15 instances (35 per cent), with similar tumors occurr in 8 pairs (53 5 per cent) The differen in age at the time of onset of symptom the pairs of twins averaged 6 3 years Int est in tumors in twins has continued [55]

HEREDITARY ASPECTS OF BREAST CANCER MOTHER AND DAUGHTER Much study centered around the incidence of breast ca cer in mother and daughter, and the clas studies of Bittner[8] have demonstrated th in mice several factors are required for t development of mammary cancer. The *h mones* control the growth and develo ment of the mammary glands, without wh mammary cancer would not result In a dition, however, there is an *inherited s ceptibility* The nature of this susceptibil has not been specifically determined, but may have something to do with the pro agation and transmission of the mamma tumor *milk agent* The milk agent, normal transmitted by nursing, has been found be filterable and sedimentable, and ca propagate in the living cell, thus it is cla sified as probably one of the filterable v ruses It is to be emphasized, neverthele that these factors have not been demo strated in human beings

Morse[51] reviewed certain of the heredita aspects of breast cancer in mother an daughter Breast cancer was considered t be perhaps the best form of cancer in ma in which to study the rôle of heredity, sinc

it is possible to diagnose the condition accurately because of its external location, rendering reports extending over many years reasonably reliable Of course, it might be said that other tumors such as that of the skin or lip are also easily diagnosed, but these cancers have been shown to be under the influence of external carcinogens For the purpose of his study, Morse selected the mother of the breast cancer patient. This was done because the sister or daughter had not usually lived through the cancer-developing age and the grandmother was often too distant for accurate recollection of facts by descendants Reports from the literature were analyzed, and it was found that 6 9 per cent of the mothers of patients with breast cancer had mammary cancer, whereas in control patients only 2 3 per cent of the mothers had mammary cancer In some series the *incidence of breast cancer* in the mothers of the cancer patients was as much as 4 times higher than that in control subjects

A second point of importance was the *age of onset* in the daughters of women with breast cancer It was found that cancer of the breast generally appeared at an earlier age in the daughter than in the mother This has been shown to be true in tumors developing in susceptible mice also Morse concluded from the review of his data at the Presbyterian Hospital in New York, as well as from other reports in the literature, that there is a specific hereditary tendency in cancer of the breast that cancer of the breast is more common in daughters of women with breast cancer than in the general population by about 3 to 1, and that cancer of the breast develops approximately 10 years earlier in the daughter than in the mother

In summary, there is considerable evidence to indicate that heredity does play a part in the genesis of certain types of tumors but even in these tumors it is usually by no means the only factor

Chronic Irritation Theory

A wide variety of conditions which cause chronic irritation have been incriminated in carcinogenesis, and that some of these are important cannot be doubted. Among the frequently encountered clinical situations are carcinomas arising in draining sinus tracts (we recently observed one in a chronically draining pilonidal sinus), in the scars of thermal burns (such a malignancy is in our hospital at the time of this writing), those following leukoplakia due to smoking, and skin cancer from excessive exposure to sunlight. In addition, there are the well known carcinogens in industry such as paraffin, shale oil, arsenic, tar and pitch, anthracene, creosote, benzene, aromatic amines, chromates, aniline dyes beta naphthylamine, ultraviolet rays, x-ray, radium, and fissionable material. In animals it is established that carbon tetrachloride produces primary cancer of the liver, urethane produces cancer of the lung and the commonly used organic solvent diethylene glycol produces cancer of the urinary bladder Finally farmers of lower Egypt may develop cancer of the urinary bladder secondary to schistosomiasis Of current interest is the experimental production of carcinoma in mice with cigarette tar,[74] with the all-important overtones of the possible rôle of cigarette smoking upon the increasing incidence of lung cancer in man It is probable that cigarette smoking is a cause of lung cancer in my opinion

In brief that certain forms of 'chronic irritation' can produce cancer is accepted by all, but precisely how this occurs is unexplained

Hormones in Carcinogenesis[61]

ESTROGENS One of the earliest suggestions that important hormonal influences might obtain in cancer was the advocation in 1889 by Schinzinger[64] of oophorectomy in premenopausal women with cancer of the breast it was believed that atrophy of the breast would follow loss of ovarian func

environment or in the cells may give rise to neoplasms Those resulting from the former, termed *conditioned neoplasms*, are known to be readily preventable and reversible, whereas the latter, named *autonomous neoplasms*, are not Many autonomous growths pass through a phase of dependent growth, and the usual trend is toward a gradual acquisition of greater autonomy Furth emphasized that the sequence of events urges greater attention to the study of normal growth-regulating mechanisms and of the very early changes in the evolution of neoplasms

THE CONCEPTS OF INITIATING ACTION AND PROMOTING ACTION—FURTHER COMMENT As stated above, the newer ideas concerning cancer formation were derived from observations that carcinogenesis, the process leading up to the first appearance of a tumor, appeared to be composed of two separate components with probably independent mechanisms In 1941 Berenblum[7] discussed these probabilities and, in examining the possible mechanism of carcinogenesis, he pointed out the significance of the co-carcinogenic action and related phenomena Again, *co-carcinogens are substances or effects which, in themselves, do not usually produce a tumor but which will produce cancer when combined with a pretreatment of the skin or some other tissue with less than the usual carcinogenic dose of a known carcinogen*

Carcinogenesis had formerly been considered a single continuous process, and the first clue of the existence of a kind of "biologic chain reaction" during the latent period of tumor development came from a study of carcinogenesis under suboptimal conditions After such suboptimal treatment, as with even a single application of a carcinogen to the skin, which normally produced only an occasional new growth, tumors could be made to develop in considerable numbers by subjecting the "pretreated" skin to several forms of stimulation which were themselves not necessarily carcinogenic Berenblum considered the effect of the limited treatment with the carcinogen as constituting the conversion of a few normal cells of the epithelium into "dormant tumor cells," which remained in a subthreshold state and required further "stimulation" for their development into progressively growing tumors The change from the normal to the dormant tumor cell came to be known as "initiating action," whereas the awakening or stimulating of the dormant tumor cells into actively growing tumors has come to be known as "promoting action" Initiating action occurs quickly and is irreversible, persisting for at least 43 weeks in the mouse In contrast, *promoting action* is slow-acting and to a degree is reversible It is important to note that tumors develop when *promoting action* follows a brief period of *initiating action* but not when the sequence is reversed

Berenblum[6] considers that *initiating action* represents a sudden, specific, irreversible change in a normal cell, whether brought about by true somatic mutation or by a mutation-like process What, then, are the mechanism and nature of *promoting action*? And how does the subsequent *promoting action* (following *initiating action*) bring about a change from dormancy to progressive growth? And what kind of biologic process is involved? In brief, it would appear that at least one explanation is that the *promoting action consists of a process of delaying maturation of cells so that sufficient stem cells may be piled up to reach the critical number of cells which are required to produce an independent colony of cancer cells* (Matured cells die off) It is known that certain cells—such as fibroblasts and monocytes in tissue culture, and also with the transplantation of various small inocula of tumor cells *in vivo*—fail to divide unless a critical number of the cells are present in close proximity

If it be accepted, for the present purposes, that delayed maturation is in truth the nature of the *promoting action*, then certain clinical circumstances are made less difficult to explain, at least tentatively. For ex-

ample, if initiating action results in a sudden and permanent change in the potentiality of a normal cell, and if promoting action by delaying maturation, allows a sufficient number of undifferentiated daughter cells of the altered cell to accumulate and thus reach a colony of critical size then neither process need be dependent upon a net increase in growth *rate* This is further underscored by the fact that some tumors continue to grow expansively though their mitotic index may even be lower than that of the parent normal tissue

Tumors are relatively rare in children possibly because of the low probability of initiating action in early life If initiating action proves to be mutational in nature then the incidence of spontaneous initiating action taking place would increase with age, as does the incidence of tumors It is thought that when a tumor does arise in a child its evolution is rapid because of the normal expansive rate of growth characteristic of that stage of development of the individual here the normal growth process itself serves as a promoting stimulus to the tumor In adults initiating action probably arises spontaneously with increasing frequency as the subject ages[53] Unquestionably many dormant tumor cells never reach the critical number required for independent growth and thus are never recognized clinically during life

DORMANT METASTASES The fact that the number of tumor cells present may be below a critical colony size and thus remain in a dormant state may explain why metastases sometimes appear in man several decades after an apparently successful radical operation for cancer

SPONTANEOUS TUMOR REGRESSION Rare but well authenticated cases of spontaneous regression of cancers do occur This might be explained on the basis that if the rate of maturation of the tumor cells were to overtake the rate of division then the number of undifferentiated tumor cells might fall below the critical size required for progressive growth. This could also explain the therapeutic arrest and regression of certain cancers when the hormonal environment is changed, such as the regression of prostatic tumors following orchiectomy and/or estrogen administration

Mechanism of Local Cancer Invasion and of Metastasis to Distant Sites (Fig 61)

The Nature of Invasiveness

In a review of the mechanisms responsible for the origin and distribution of blood borne tumor metastasis Coman[15] pointed out that two distinguishing biologic characteristics of malignant tumors are their ability to invade adjacent normal tissues and their ability to produce secondary tumors in distant parts of the body Local tissue invasion was emphasized as a prerequisite to the formation of blood borne metastasis, for in this way tumor cells gain entrance to the vascular system initially Therefore, an understanding of the mechanisms of metastasis begins with inquiry into the phenomenon of invasiveness

By invasiveness is meant the ability to penetrate surrounding tissues This capacity is not restricted to malignant cells, since leukocytes and macrophages may also enter other tissues Nevertheless the capacity to invade other tissues is a characteristic peculiar to certain cells only and is a biologic attribute not shared by cells of benign tumors or by most normal cells other than leukocytes and macrophages Moreover, the invasive properties of tumors appear to reside largely or entirely in the tumor cells themselves Coman concluded that factors such as multiplication rate liberation of lytic substances and loss of growth restraints need no longer be regarded as essential factors in invasiveness, since these qualities either are shared by noninvasive tumors or do not exist in malignant tumors What then, are the properties peculiar to leukocytes macrophages and cancer cells which permit invasion?

It would appear that this property of invasion depends on there being present isolated single cells and on a highly developed

ameboid motility It was reported as early as 1863 by Virchow[71] that cancer cells possess ameboid motility, and this has been amply confirmed by tissue culture studies in modern times By photographic means,[20] cells from breast cancers were shown to have an average speed of 0 7 μ per minute, with a maximum rate of 2 4 μ per minute Cells from a carcinoma of the kidney attained a maximum rate of 4 4 μ per minute, while cells from a mouse fibrosarcoma traveled at 6 2 μ per minute Of further interest was the observation that even tiny clusters of from 3 to 5 epithelial cells from a rabbit carcinoma progressed as an ameboid unit It was also demonstrated that cells of benign epithelial tumors and even non-neoplastic glandular epithelial cells (from cystic disease of the breast) may be motile in tissue culture, *provided that these cells are first forcibly detached from their companion cells*

An important capacity for local invasiveness of cancer cells, then, would appear to be their ability to progress by ameboid movement The reason that the cells of normal tissues and of benign tumors usually do not invade surrounding tissues would appear to be that they are so firmly attached to one another that they are unable to escape and begin their ameboid migration In contrast, the cells of malignant tumors are often found in the body free from the parent tumor It was shown by Coman[14] that the magnitude of force required to separate a pair of normal squamous epithelial cells from each other is much greater than the force required to separate cancerous squamous cells Furthermore, it was possible more easily to dislodge individual cells of various malignant adenocarcinomas from man by a mechanical shaking of the cancerous tissues than was the case with the shaking of normal prototype tissue, from which few cells were dislodged[15]

This lowered adhesiveness of cancer cells was related by Coman and his associates to a deficiency in calcium, and it was concluded that the local invasiveness is associated with, if not due to, this deficiency Coman noted that most cell physiologists agree that calcium is located principally at the cell surface, but how it is combined there and why the cancer cell is unable to bind the normal amount of calcium are as yet unknown

RELATION OF INVASIVENESS TO METASTASIS Indirectly quoting Coman[15] further, after the cancer cells have separated from one another and begun to travel by ameboid motion through the tissues, they tend to follow paths of least resistance Loose tissues such as muscle and areolar tissues are more readily invaded than hard and compact tissues such as bone and cartilage It is pointed out that cancer of the prostate infiltrates the loose tissues of the nerve sheaths in preference to the denser parts of the gland itself, and that lymphatics offer natural preformed paths of low resistance Indeed, cancer cells may even grow in lymphatics as solid cords or be carried along in the current as individual units Similarly, cancer cells in general have little difficulty in penetrating the walls of capillaries and veins (one often sees hypernephroma occluding the renal vein), whereas invasion through the muscular wall of an artery is rarely observed Once the veins and capillaries have been invaded, the blood stream may readily carry the cells to different parts of the body In fact, tumor cells can commonly be demonstrated in the venous drainage of a tumor and even, though far less frequently, in the peripheral venous blood They may be particularly well demonstrated by bone marrow biopsy (Fig 61)

Mechanisms of Blood-Borne Metastasis

Of particular importance in the spread of tumors by way of the blood stream are the factors which determine the number and anatomic distribution of the metastatic tumors produced by the primary growth The answers to these factors have to do with the site of arrest of the embolic tumor cells (the organ involved), the survival of arrested embolic cells (is the "soil theory" more valid than the vascular "distribution"

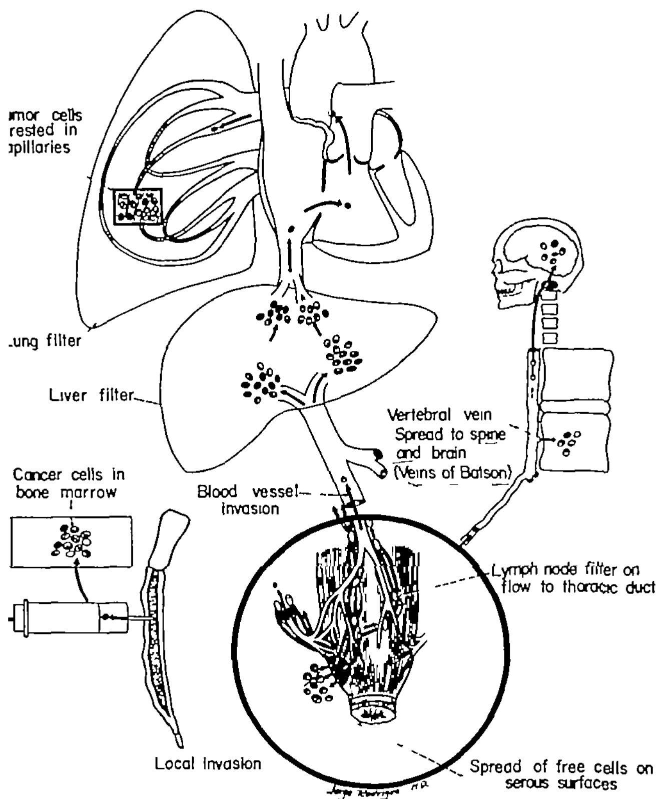


Fig 61 It is metastasis which precludes successful surgical management of a great many tumors The actors which inhibit and those which promote metastasis are of fundamental concern

ieory?), and the subsequent growth of the ew tumor

As with the injection of bacteria into the lood stream to produce a bacteremia, the umber of embolic cells is an important factor in producing a significant number of distant metastases in fact a direct proportionality exists in this respect. Of course the mortality of embolic cells is high, and only a small percentage of those which

break away and enter the blood stream find nourishment elsewhere and produce secondary tumors

Next, what factors in the primary tumor influence the number of tumor cell emboli released into the circulation? Zeidman, McCutcheon, and Coman[76] found that the number of metastases was proportional to the duration of growth of the primary tumor There was a poor correlation between the size of the tumor and the number of metastases, and this has a parallel in man in that it is a well established clinical and pathologic fact that the number of metastatic tumors in man bears no particular relationship to the size of the primary tumor

Factors Affecting the Distribution of Metastatic Tumors

As noted above, there have existed two major hypotheses regarding the location of metastatic tumor emboli the *soil theory* and the *circulation* or *distribution theory* Essentially, the soil theory holds that certain organs are more conducive to the arrest and growth of embolic cells, with the production of secondary tumors, than are other organs The proponents of this theory have pointed to the fact that the lungs, liver, and bone are frequently involved, whereas muscle and the spleen were not frequently involved The alternative hypothesis has been that most metastases could be explained simply on the basis of the distribution of blood containing the tumor emboli

Coman and his associates[15] showed that whereas one would expect the lungs and the liver to contain a large number of secondary tumors—the portal blood draining through the liver and the systemic blood through the lungs—the fact that the bones of the spine were commonly involved by metastases from the prostate (owing to the veins described by Batson[4]) weighed heavily in favor of the distribution theory Further to examine this phenomenon, suspension of tumor cells injected into the femoral veins of rats and rabbits were diverted into the vertebral veins, thus producing tumors in the vertebrae[16] From these studies it was concluded that the three common foci for metastatic tumors—the lungs, liver, and the bones of the skeletal axis—are situated as might be anticipated on the basis of the "blood flow" theory

How Are Arterial Metastases to Kidneys, Adrenals, Spleen, and Muscle Explained

It is considered probable that, first, cells may break off as pulmonary secondary metastases and spread to these organs Second, it was shown by Prinzmetal and his associates[59] that glass beads of a size larger than most cancer cells pass readily through the lungs, probably through arteriovenous shunts (Fig 174) Third, it was shown that if tumor cells are injected into the left heart and thus allowed to spread to the organs not usually involved by metastasis, metastases readily occur, again emphasizing the importance of the circulation in the distribution of embolic tumor cells and the formation of secondary tumors Apparently in conflict with the blood flow theory, some organs did not exhibit metastatic takes as readily as did certain other organs, even when approximately the same number of embolic cells reached the organs in question. However, it was noted that the cells that lodged in arterioles usually did not take root and multiply, while those that lodged in capillaries took root much more often When the various organs were compared on the basis of the number of embolic cells found lodged in capillaries, there was a good correlation

Nevertheless, there do appear to be some as yet unexplained differences in the incidence of tumor takes in different tissues

Coman[15] considered it possible that the fact that the lung is essentially an "air-filled sponge," in contrast to the solid structure of other organs, may render it more difficult for tumor cells to secure blood supply and to grow readily, moreover the lung is continually expanding and contracting He noted that while the lung is the most frequent site of metastatic tumors, still it must

-ive a relatively enormous number of -boli, compared with those that reach -er organs Should only a few of these -boli survive in the lungs, it would be ex-ted that the lung would still be the organ -st commonly the site of metastasis

-her Factors in Tumor Spread and Re-rrence

-YMPHATIC METASTASIS Various consider-ons of lymphatic metastasis have been -iewed by Willis[73] and by Taylor and -thanson[69] The lymphatics constitute nat-l and preformed channels of least re-tance for tumor emboli Cells enter the -ipheral channel of the first lymph node, -dually overwhelm that node, and break -ough to the next node in line. Occlusion -axillary nodes by metastatic breast cancer -ults in lymphatic back pressure render-; involvement of the internal mammary -des more likely In an as yet poorly ex-ined manner the lymph nodes appear to -ovide not only a mechanical but also an -munologic barrier to cancer

-SPREAD OF TUMOR DURING COLON RESECTION -le[13] called attention to the fact that a re-rrence following a colon resection may be -e to the circumstance that manipulation -the tumor pushed cells backwards into -wel that was later used to perform the -astomosis with tumor cell implantation -ong the suture line In addition it has been -own that the veins leading away from a -rcinoma of the colon (and from most -her cancers) often contain tumor cells, -d it is advisable first to ligate the blood -pply to the involved portion of the colon -ligature is also tied firmly around the -lon at a judicious distance above and -low the tumor to prevent the mechanical -ssemination of tumor cells into the bowel -at is going to be left behind

In another connection Garlock and his -sociates[29] showed that merely to brush a -onge across the serosal surface of the -wel at the site of a carcinoma of the colon -ll pick up cancer cells It is probable that metastasis readily results throughout the peritoneal cavity in this manner

The *air borne spread* of tumor was demonstrated experimentally by Furth[26] and, more recently by Norman and McBroom[54]

General Effects of Cancer upon the Patient

Malignant Cachexia

Most cancer patients do not die from the *mechanical* effects of the primary tumor and the metastases—they die from the *malignant cachexia* that develops The clinical picture of malignant cachexia is only too familiar, including the wasted face, sallow and anemic complexion the languid demeanor, weight loss, lack of energy, loss of appetite and, terminally, various infections Yet in a syndrome which is so characteristic of advanced malignancy (or of advanced starvation and infection), it is surprising how difficult it is to pinpoint physiologic mechanisms which have been deranged and which have resulted in this state of physiologic disarray Infection and malignancy have many similarities (Fig. 62)

There are at least two major schools of thought regarding the mechanism of malignant cachexia The first school holds that the cachexia results from the fact that the tumor withdraws from the body some substance which is essential to good health The

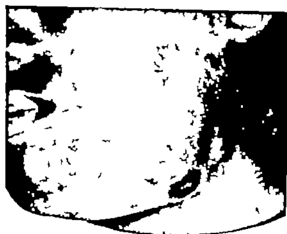


Fig 62 Infections and malignant tumors have many similarities This patient was thought to have a pyogenic or fungus infection but biopsy revealed a sarcoma

second school—and this is the one which appeals to us more strongly—holds that the tumor produces some substance or substances which adversely affect the more subtle functions of many of the organs of the body, in particular the liver and the processes of blood formation

Weight loss and poor nutrition are hallmarks of advanced cancer, but it is not always clear whether the weight loss is due to the loss of appetite or whether the weight loss would have occurred anyway even had the patient been force-fed The fact is, while an increased intake may improve some individuals, many cancer patients have been force-fed and have still not been able normally to utilize the materials which were introduced into the gastrointestinal tract Therefore, in addition to the inadequate intake that may result from loss of appetite, there exists also the additional circumstance that the food taken in is not normally utilized in the fabrication of tissue The mechanisms of, first, the loss of appetite and, second, the loss of the ability of body cells to utilize normally the ingested foodstuffs are by no means clear

An additional finding in advanced malignancy is that of anemia In a series of studies, Wintrobe[11] found that not only is hemoglobin formation deranged in the presence of chronic infection but that the life span of the individual red cell is shortened Patients with severe chronic infection and those with chronic cancer have many clinical findings in common, and one of these is the development of anemia of a more or less severe degree As Wintrobe has shown for infection, others have shown for cancer For example, Sheets and his associates[65] found that three patients with carcinoma of the cervix uteri who had normal erythrocyte levels and normal rates of red cell loss developed a random destructive mechanism for transfused cells from 7 to 10 days after x-ray therapy was begun They exhibited various grades of oligocythemia, which were ascribed to excessive loss of erythrocytes from random destruction, despite actual acceleration of the rate of erythrocyte release to the circulation A fourth patient with the same disease was demonstrated to have a *spontaneous* random destruction mechanism for transfused cells, but she maintained a normal erythrocyte level by an accelerated rate of red cell release These workers were not able to demonstrate a depression of the rate of red cell release from the bone marrow in this particular cancer

Clinically, carcinomas of the cecum and ascending colon, more particularly the former, are notoriously apt to be associated with an anemia which is frequently difficult to explain on the basis of blood loss, particularly when virtually no bleeding has been noted and no occult blood can be demonstrated in the stools Certainly the degree of occult blood detection is not proportional to the profound anemia which these patients may have It is not difficult to suspect the possible presence of not only an increased rate of red cell destruction but also a depression of the bone marrow in these subjects, though such has not usually been demonstrated Needless to say, the anemia of chronic cancer may be due in part to nutritional inadequacy and, more rarely, t bone marrow replacement by metastases

Chemical Changes in Cancer

Despite a prodigious amount of chemic investigation in recent years, the most con sistent chemical finding is that of a de creased catalase activity in the liver in th presence of a rapidly growing malignancy The function of this enzyme is to catalyz the union of hydrogen and oxygen to form water Lucké and his associates[43] showe that this capacity of a tumor to produce reduction in the liver catalase activity crossed the parabiotic union, a finding which suggested that a cancer in one animal probably did elaborate a substance that depressed hepatic function in the liver of the other Of course, such a preparation did not entirely exclude the possibility that the tumor removed from both rats some sub-

stance which resulted in a lowering of the liver catalase activity

Remote Effects of Certain Tumors

Elsewhere it has been mentioned that certain tumors of the lung, most particularly the localized fibrous mesothelioma of the pleura may result in osteoarthropathy This may assume the form of attacks of chills, chilly sensations or fever, painful and sometimes migratory involvement of joints, and clubbing of fingers or toes or both[12] Moreover, the joint manifestations usually disappear promptly, even within days, after the mesothelioma is removed The mechanism by which these joint symptoms and signs are produced is obscure

Physiologic Considerations in the Treatment of Cancer

The Unpredictability of the Individual Tumor

One of the most difficult matters in the standardization and the evaluation of surgical therapy—and, indeed, of all forms of therapy—of malignant tumors in man lies in the fact that human tumors vary so greatly in their natural history This is due first to the fact that few tumors are identical, that is the setting is not the same as when one transplants in laboratory animals a standardized tumor from strain to strain and from generation to generation. The second difficulty lies in the fact that the internal environment for a particular tumor varies from one person to another Thus the major variables of the tumor itself and of the host cannot be controlled in man This is particularly true of certain cancers such as those of the thyroid, breast, and stomach The bizarre behavior of thyroid cancer has recently been emphasized by Duncan Cantril and Lund.[19]

The importance of *biologic predeterminism* in gastric carcinoma as a limiting factor of curability was emphasized by MacDonald and Kotin[44] in an analysis of recent reports regarding the operability and cure of this neoplasm. They concluded that it is biologic predeterminism, rather than the time or type of surgical treatment, which governs the end results in gastric cancer Natural selection was the best indicator of operability and possible resectability In general, patients with well defined symptoms of gastric dysfunction presented the most favorable tumors Duration of symptoms bore some relation to resectability, and curability increased with duration of symptoms in resectable cases The pathways of local and regional spread were considered to be such that total gastrectomy offered no promise of increase in curability The only genuine "early" treatment is gastric resection for gastric ulcer which may represent carcinoma Radical, extended surgery will be curative for some locally invasive lesions infiltrating adjacent structures without evidence of remote metastasis but the available evidence indicates that under the most ideal circumstances, less than 20 per cent of all gastric cancers are surgically curable MacDonald and Kotin concluded that the most satisfactory procedure, by the criteria of curative and physiologic end results, is genuine subtotal gastrectomy with wide omental resection and splenectomy

A similar line of reasoning applies to the treatment of carcinoma of the breast.

The Hormonal Therapy of Cancer

CARCINOMA OF THE PROSTATE. Before considering specific cancers, it is desirable to survey briefly the steps which have led up to the present status of endocrine therapy in cancer As pointed out earlier oophorectomy has for more than 50 years been advocated for the control of mammary carcinoma. Furthermore, it has long been appreciated that various types of tumors of the female genital tract may be induced by the administration of estrogens, at least in laboratory animals

The rôle of androgens in maintaining normal prostatic growth and function in dogs was first demonstrated by the classic studies of Huggins.[33] Later, in 1941 he and his as

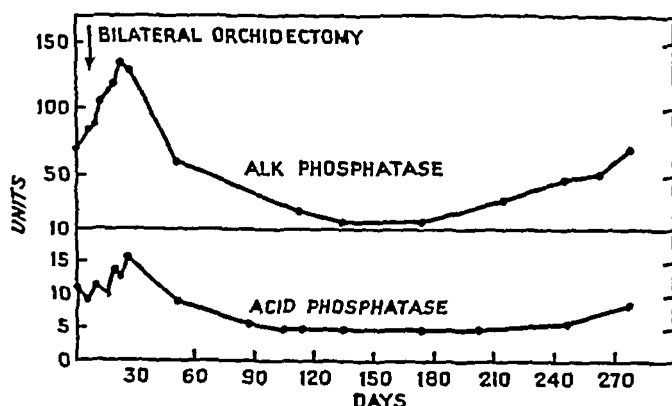


Fig 63 Effects of castration on serum alkaline phosphatase and serum acid phosphatase in case of carcinoma of prostate Androgens are necessary for normal prostatic growth Prostatic carcinoma often produces an elevation in the acid phosphatase level This level usually falls following orchiectomy or estrogen therapy, but can be made to rise again by giving androgens (From HUGGINS, C Harvey Lectures, 42· 188, 1947, as modified by Wright, S *Applied Physiology* Ed 9 London, Oxford University Press, 1955)

sociates[35] reported their studies regarding the effects of castration on advanced carcinoma of the prostate gland In their original report of 21 cases in which castration was performed, 4 died within 8 months of operation, and in 2 the operation was too recent at the time of writing to permit evaluation, but in 15 cases prompt clinical improvement had occurred This was evidenced by a decrease in the serum acid phosphatase level (Fig 63) in all but 2 cases, an increase in weight and a return of appetite, an increase in the red cell count of the peripheral blood, a decrease in the amount of pain from the primary or the metastatic lesions, a shrinkage in the primary lesion, an increased density of metastatic lesions visualized by roentgenogram and, in 1 case, an improvement in neurologic signs of compression of the cauda equina by metastasis It was later shown that estrogen therapy produced similar results The injection of an androgen such as testosterone, on the other hand, caused a recrudescence of the pain and a rise in the acid phosphatase level

Adrenalectomy for prostatic cancer was first reported by Huggins and Scott in 1945[71] The reasoning behind this procedure was that relapse in patients who had been initially improved by orchiectomy and estrogen therapy was due to the secretion of androgens by the adrenals In a subsequent and more extensive review of such studies, Huggins and Bergenstal[32] reported their observations on adrenalectomy in 7 patients with metastatic cancer of the prostate whose disease had relapsed following previous responses to antiandrogenic therapy One patient died postoperatively, but in 4 others some of the following effects were observed relief of intractable bone pain, a gain in body weight, and a reduction in the serum acid phosphatase level In 2 patients there was a significant shrinkage of large nodular prostates, and in 2 patients no improvement occurred

Other teams at various medical centers have since also investigated adrenalectomy for reactivated carcinoma of the prostate In general, the results have been disappointing Transient relief of pain is commonly observed in the majority of patients, but these results are usually short live and the progression of the tumor is affecte in but few Nevertheless, these studies hav shown again that alterations in the hor monal balance can and will influence th natural history of certain malignant tumor

Whereas the relief of pain from prostati cancer is usually prompt following castra tion, that obtained with diethylstilbestr is more gradual A dosage of 5 mg 3 times a day may be employed, but care must b exercised to avoid excessive fluid retention lest heart failure be precipitated Th mechanisms by which castration and stil bestrol effect their improvement in ad vanced prostatic malignancy are still un certain As a practical point in prognosis however, it is worth remembering that the serum acid phosphatase level usually varie with the course of the disease, falling a the beneficial effects of castration and estro gen therapy are realized and rising again as the efficacy of this therapy begins to wane

CARCINOMA OF THE BREAST [37] Earlier in thi chapter it was stated that Schinzinger

the first to suggest castration for cancer of the breast and that Beatson[8] first reported, in 1896 the castration of 2 premenopausal women who had advanced metastatic cancer of the breast Relief of pain and regression of the malignant growths in these patients were observed In 1936 Dresser[18] reported on a series of 59 patients whose ovaries had been treated with what was supposed to be destructive doses of x ray Beneficial effects were reported in about one-third of the cases though subsequent reports by others did not claim quite so high a percentage of successful results In 1949 Treves[70] reported the results of castration in 13 male patients with advanced carcinoma of the breast and the results in this group were just as favorable as those in women regression of local lesions and healing of skeletal metastases being observed

In 1939 Nathanson and Andervont[52] reported that the prolonged administration of testosterone to female mice of a high mammary cancer strain resulted in a significant decrease in the number of mammary tumors that ultimately developed and only a short time later Farrow and Woodard [4] reported the treatment of metastatic cancer of the breast with testosterone Since then considerable palliation has been achieved in premenopausal women by the administration of androgens particularly following oophorectomy Testosterone propionate may be given in doses of 100 mg intramuscularly 3 times a week. Adair and others [1, 2] found that an average cumulative dose of 3000 mg. was required before objective improvement in skeletal metastases was noted They found that such therapy produced objective improvement in 19 per cent of 48 patients with skeletal metastases and 15 per cent of 54 patients with extraskeletal metastases Temporary relief of pain was obtained in 44 of 58 patients in whom this was the initial complaint. It was particularly significant that certain patients were symptomatically improved even in the presence of progression of the disease.

In the administration of androgens care must be taken to avoid dangerous elevations in the serum calcium level This level may be somewhat elevated even at the time testosterone therapy is begun, but if it begins to rise under therapy the hormone should be stopped at once In addition, excessive fluid retention caused by this therapy may result in cardiac decompensation

Estrogen therapy in mammary carcinoma In 1944 Haddow and his associates[31] demonstrated a therapeutic effect of estrogens in postmenopausal women with advanced mammary carcinoma Since that time numerous others have reported on the use of this therapy The criteria for the administration of estrogens in advanced breast cancer are somewhat different from the indications for androgen therapy Whereas androgens have their greatest effect on osseous metastases in premenopausal women, estrogens have their major beneficial effect on soft tissue lesions in postmenopausal women Lesions of the skin, lymph nodes, pleura and breasts may be expected to show improvement in roughly one fourth of the patients with this type of disease The dosage of diethylstilbestrol employed varies from 5 to 30 mg per day, with an average dose being about 15 mg by mouth Adair and his associates[2] found it necessary to administer approximately 630 mg before the average patient obtained relief, which lasted from 2 to 17 months Pain was relieved in slightly more than one-half of the patients with this complaint

Patients treated with estrogens frequently experience a definite improvement in their general physical condition. Their sense of well being is enhanced, blood formation is increased appetite is improved, and most of them gain weight. Unfortunately early recurrence of symptoms is the rule

Bilateral adrenalectomy for advanced mammary cancer Huggins[32] first advanced adrenalectomy as a treatment for metastatic disease of the breast. In brief he speculated that certain mammary cancers are dependent upon adrenal estrogens for growth. When the neoplasm is *adrenal-dependent,*

bilateral total adrenalectomy is often followed by regression of the metastases with reossification of the bone defects Symptomatic improvement with relief of pain may be marked Metabolic studies were performed by Pearson and co-workers [58]

Unfortunately, only a comparatively small percentage of mammary carcinomas appear to be adrenal-dependent, and it has not been possible to predict in advance those which will regress after adrenalectomy Nevertheless, when the other more well established endocrine measures have been exhausted in patients with advanced metastatic mammary cancer, bilateral total adrenalectomy may produce considerable improvement in perhaps one-fifth of the cases This therapy is of course not curative

Use of ACTH and cortisone in treatment of terminal malignancy Pearson and his associates[57] found that cortisone produced objective remissions in some patients with breast cancer, for short periods of time Various workers have commented upon the use of ACTH and cortisone in terminal malignancy and the report by Raab and Gerber[60] is representative Their experience with the use of cortisone and ACTH in the management of incurable malignancy indicated that it should be used only in those patients in whom all known modalities for cure had been abandoned and for whom only large doses of narcotics remained In such patients cortisone and ACTH brought about an improved mental state and better nutrition, and reduced the amount of narcotics required for pain They also often rendered it possible for a patient with a hopeless neoplasm to maintain a more normal existence for a longer period of time

Hormonal Influences upon Other Types of Tumors

THYROID CANCER The reports of Rawson[61, 62] and of others emphasized that the metastases of thyroid cancer could be induced to take up more radioactive iodine by either total thyroidectomy or the administration of thiouracil Reporting upon 100 cancers of the thyroid, Rawson and Rall[63] found that 46 possessed the capacity to concentrate radioactive iodine, but that none of these tumors was capable of concentrating more than a fraction of the iodine trapped by normal thyroid tissue However, in approximately 50 per cent of 52 patients, total thyroidectomy increased the function of previously nonfunctioning metastatic lesions, the metastases were capable of maintaining the patient in a euthyroid state and they took up radioiodine Moreover, the administration of thyrotropic hormone (TSH) induced function in the tumors in about one-third of the cases studied Finally, it was demonstrated in 62 per cent of a series of 42 previously totally thyroidectomized patients having skeletal or pulmonary metastases that the prolonged administration of thiouracil or of Tapazole, agents which augment the action of the thyrotropic hormone, resulted in the metastatic lesions' acquiring maximum capacity to concentrate radioactive iodine This suggested the practicability of effectively treating the metastases with radioiodine Unfortunately, the of radioiodine for this purpose has been appointing

THE EFFECT OF ACTH AND CORTISONE U LYMPHOID TISSUE Scarcely had ACTH cortisone become available than it was parent that these agents were strongly l for lymphoid tissue In 1949 Pearson his associates[56] reported their expe in the treatment of certain lymphoid tis with ACTH and cortisone Frequently enlarged nodes virtually melted away o the course of 2 or 3 days, and the marke elevated white cell count fell to within n mal limits Similar findings were repor by others Lymphocytic leukemia was most specifically affected by such thera myelogenous leukemia being consideral more refractory Nevertheless, such rem sions proved to be temporary and early currence was the rule

Concluding Remarks—Cancer Chemotherapy[22]

The treatment of human cancer is the center of intense activity at the present time It is now acknowledged that with surgery and radiation therapy alone one cannot hope to cure the majority of tumors, and that chemotherapy must be rendered more effective. While most drugs are even less effective than radiation and surgery, a prodigious clinical survey of possibly effective anticancer agents is being carried forward under governmental auspices The hope is that *effective cancer control measures* need not await the ultimate explanation of the processes of carcinogenesis

The chemotherapeutic agents which are being used against tumors may be classified in four groups

1 Cytotoxic agents
2 Alkylating agents
   a. Nitrogen mustard
   b Thio-TEPA (triethylene thiophosphoramide)
   c Myleran
3 Antimetabolites
   a Folic acid antagonists
   b Antipurines
   c Antipyrimidines
   d Antiglutamic acids
4 Hormones
   (Examples given above)

ALKYLATING AGENTS Particular interest at the present time centers upon further study of nitrogen mustard (HN_2) and related compounds which have a *radiomimetic* effect. That is the physiologic changes produced by these chemotherapeutic agents are similar to those produced by radiation There is serious depression of the bone marrow, and thus dosage must be carefully controlled.

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Chapter 8

Radiation and Radioactive Isotopes

There are many reasons why a brief consideration of ionizing radiation *per se*—as well as the experimental, diagnostic, and therapeutic uses of radioactive isotopes—should be included in this volume The most practical reason is, of course, that the use of these agents in surgical diagnosis and treatment comprises a major facet of surgical practice A second reason one chooses to discuss "x-ray and isotopes" is that it affords an opportunity to illustrate that the disciplines of physics, chemistry, and biology all have a stake in the effects of ionizing radiation The modern experimental physiologist must know something of all these sciences, and they are used daily in various spheres of surgical endeavor

Radiation

The literature in this field is already voluminous and is increasing by leaps and bounds The following discussion is based to a considerable extent upon the comprehensive reviews of Sparrow and Rubin[13] ("Effects of Radiations on Biological Systems"), of Ord and Stocken[10] ("Biochemical Aspects of the Radiation Syndrome"), and of Patt[11, 12] ("Protective Mechanisms in Ionizing Radiation Injury," and "Radiation Effects on Mammalian Systems") These several publications, reasonably complete in themselves, offer large bibliographies which may be consulted for further information in this field

Historical Aspects

To appreciate that the science of radiation is a relative newcomer to the family of physical and other natural sciences, it need only be recalled that Wilhelm Konrad Roentgen did not discover x-rays until 1895 In the following year Henri Becquerel reported his discovery that uranium emitted a type of ray without exposure of the material to light rays This report, when read by Marie Curie and her husband, Pierre, initiated a series of studies beginning in 1897 which culminated in a report of the probable existence of a new element, published in the Proceedings of the French Academy of Science in 1898 Forty-five months later, on July 18, 1902, Pierre and Marie Curie announced the preparation of a decigram of pure radium, estimating the atomic weight of the new substance to be 225[1]

Since these initial discoveries the use of x-ray has become a cornerstone of medical practice, and literally hundreds of both stable and radioactive isotopes have been isolated

Types of Radiation

In Figure 64 are shown the wavelengths of the spectrum with an indication of the biologic effects which each type of wave may have upon the organism For example, it may be seen that the Hertzian and infrared rays produce mainly thermal effects whereas, at the extreme left of the spectrum, gamma rays produce important chemical effects which will be described in more detail below Observe that x-rays merge with gamma rays, though gamma rays are derived from a variety of sources Still further to the left, though not indicated here, are cosmic rays, which have the shortest

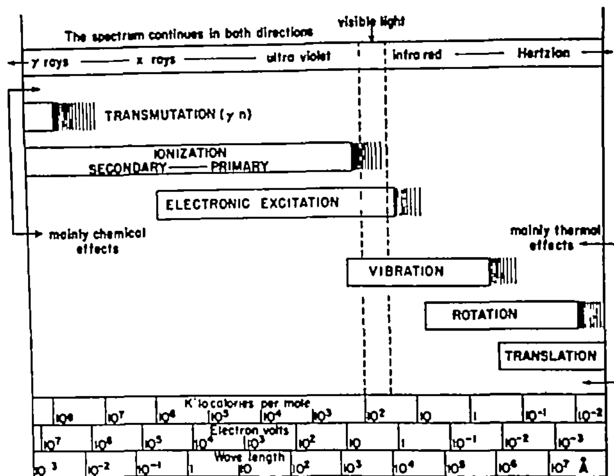


Fig 64 The spectrum and the effects produced (From SPARROW A H., AND RUBIN B A In *Survey of Biological Progress* Volume II New York Academic Press, Inc., 1952) At the right the infrared portion of the spectrum produces mainly thermal effects As ultraviolet merges into x-ray ionization occurs and chemical effects are produced The wavelengths are given below Note how little of the spectrum is visible to the naked eye

wavelength of which there is knowledge There is some evidence to indicate that cosmic radiation and natural radioactivity may have effects on human mutation and this has further been noted in studies revealing the carcinogenic effects of these rays Moreover, some workers have claimed biologic effects not only from infrared but also from high frequency radio waves The effects of ultra violet rays have been extensively investigated.

Note in Figure 64 how little of the spectrum is visible to the naked eye

SOURCES OF THERAPEUTIC RADIATION The equipment available for the administration of x rays has increased enormously both in power and efficiency and by use of appropriate filters it has been possible to obtain almost monochromatic bands from x ray tubes Since the biologic effects of x rays and gamma rays are virtually identical it is permissible to consider them together The difficulties in handling isotopes—and their short half lives, in many instances—render such sources of radiation impracticable at the present time This problem has partly been solved by the use of cobalt units, they have a long half life and provide almost monochromatic gamma radiation

ALPHA RAYS, BETA RAYS GAMMA RAYS, AND X RAYS The clinician commonly encounters discussions of ionizing radiation in which it is stated that such and such an isotope is an alpha emitter, a beta emitter or a gamma emitter—or a combination of two or more of these Since for practical purposes the gamma rays and the x rays may be considered as being approximately identical let us first define alpha and beta rays

The *alpha ray* consists of a heavy particle, that is it has a high density (Fig. 65) Since the particle has a high density or weight, it

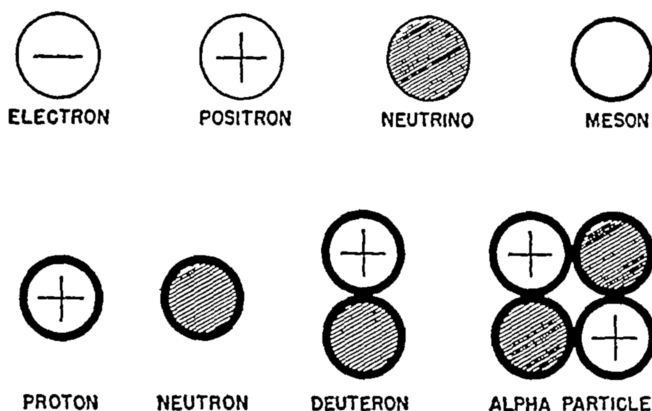


Fig 65 Schematic representation of subatomic particles and some of their combinations Most of these particles have important biologic and therapeutic potentialities (From GLASSER, O, QUIMBY, E H, TAYLOR, L S, AND WEATHERWAX, J L *Physical Foundations of Radiology*, Ed 2 New York, Paul B Hoeber, Inc, 1952)

has a relatively low velocity While such particles or rays may have a considerable biologic importance because of their "ionization densities," they are able to penetrate only superficially, in contrast to the lighter ions (of less mass), which travel rapidly and penetrate more deeply Alpha particles have a positive charge and represent the helium nucleus

Beta rays are negative electrons, and they have an intermediate position between the heavy alpha particles and gamma rays Beta rays have been shown to simulate the effects observed with alpha particles, but for a given energy the beta particles or electrons travel at a greater velocity than do alpha particles and have much longer paths of penetration Alpha particles, protons, and deuterons dissipate energy in straight lines of high ionization density, while beta particles scatter their energy more thinly over a tortuous path [13]

The third major type consists of x-rays and gamma rays, they have a low ion density or weight, and produce a picture which is in marked contrast to that of the heavy alpha particles X-rays and gamma rays have a much greater penetrating effect and travel at a higher velocity These are electromagnetic quanta, not particles

Thus, superficial lesions may be treated with isotopes emitting alpha or possibly beta particles, but deep tumors must be treated with gamma emitters

From the brief foregoing comments regarding the types of radiation which may be achieved with various wavelengths or particles in the spectrum, including combinations of these, it is clear that one can achieve a variety of effects With the use of a single one of these, such as the x-ray, one can alter the biologic effect by varying the intensity, the total length of exposure, and the timing of the component periods of the total exposure Some of the means by which the physical energy of the x-ray is transferred to a biologic preparation—and the means by which the biologic preparation reacts to produce chemical, physiologic, cytologic, and genetic changes—will now be examined There is indeed a conservation of energy or mass as the velocity and mass of the rays are dissipated, the kinetic physical energy is converted into chemical energy by producing chemical changes within the target material

It has been seen that the energy waves which one may direct toward a biologic system cover a vast range of qualitative and quantitative possibilities, furthermore, biologic preparations vary greatly in their responses to a given energy dose Small wonder that it is often difficult to compare data from different laboratories To permit comparison, both the radiation and the system bombarded must be rigidly controlled, and this is still not always done The ideal situation would be to determine the linear energy transfer in terms of ergs per gram of tissue irradiated This is not yet possible

Mechanisms of Radiation Energy Transfer[13]

If there are many types of radiation, there are also various types of energy transfer mechanisms For example, radiations whose energies are below 1 electron volt, such as infrared and radiowave, rarely cause changes at a chemical level, for their energy is below that of most chemical (electron) energy states It is difficult to prove that biologic effects which have been reported for

these radiations do not result from purely thermal effects

Referring to Figure 64, it is seen that as one advances from the region of visible light toward the ultraviolet, chemical changes become possible and effects become more marked When energy of the shorter wavelength radiation is absorbed by the target substance—and energy that is not absorbed has no effect—a photochemical reaction occurs in several connected stages The first of these is the absorption of the radiation by the molecule to become an 'excited molecule, the second stage being either the decomposition of the molecule or the re emission of the energy by fluorescence collision or chemical reaction, the third stage may represent continuation products of the second stage perhaps secondary reactions such as molecular rearrangements chain reactions, polymerization, or depolymerization. Absorption of the shorter wavelengths may be increased by adding a photosensitizing substance to the absorbing medium though strong absorbing groups which render a molecule more sensitive are not necessarily the points of chemical change

The Concept of Ionization[13]

In the simplest terms, *ionizing radiation separates the target molecule into ions or removes an ion from the molecule* In general, while ultraviolet light (Fig 64) is sometimes capable of ionizing the molecules of the target substance by completely ejecting an orbital electron (Fig 66), ultraviolet light is not commonly thought of as a respectable member of the family of ionizing radiation. Even so the wavelengths of the spectrum are continuous, and the divisions between them can only be arbitrary with respect to energy transfer or penetration properties. With gamma or x rays a fraction of the energy produces *excitation*, giving rise to processes that are primarily photochemical, and these comprise an important source of certain radiochemical events Nevertheless, the *ionizing effect* is the predominant one.

The ionizing effect of x rays is a complex process The higher energy x rays can readily ionize a molecule by imparting to the molecule sufficient energy to eject completely an orbital electron (the photoelectric effect), more important, the energy is such that the ejected electrons are given so much momentum that they go on as independent particles to produce *secondary ionizations* (Fig 66) that are so extensive as to outweigh the importance of the initial impact of the x ray upon the original molecule The ejected electron travels at a speed which is determined by the impact of the original x ray, minus the power with which the electron was bound to the molecule originally

It is apparent that when the structure of an atom has been changed by altering the electron composition, a substance of different chemical properties will have been produced in short, the physical or x ray energy has been transformed into chemical energy

Biochemical Aspects of Radiation Changes: Further Discussion

It is no longer enough merely to note the biochemical effects of x rays in general terms, for there is a growing body of information which demonstrates that certain specific and other somewhat less specific chemical effects are produced regularly under a given set of radiation circumstances Several instances of this may be noted. For example when water freed of oxygen is bombarded with alpha rays a marked production of hydrogen peroxide occurs In contrast passing x rays through the solution has no effect, that is, no hydrogen peroxide is produced The production of these changes in water appears to be a function of the ionization density for while high energy gamma or x rays produce almost no reactants alpha rays cause a rapid evolution of oxygen and hydrogen. Beta particles generally produce intermediate amounts of the gases depending upon their energies

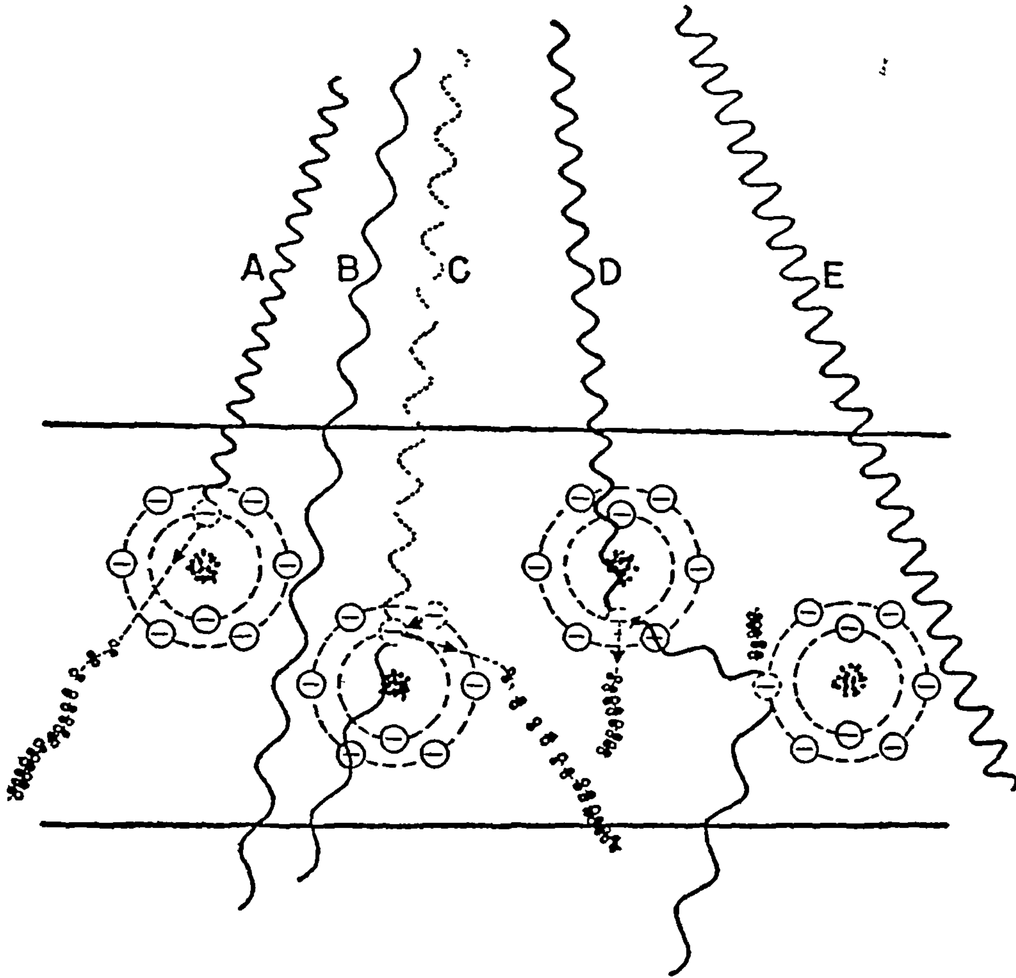


Fig 66 "Interaction of radiation and matter Roentgen-ray photon *A* strikes an electron of the *K*-orbit of an oxygen atom, it utilizes part of its energy for the removal of the electron to the exterior of the atom and imparts the remainder of its energy to the electron, giving it a high velocity This is a photoelectric absorption and the removed electron is a photoelectron This photoelectron travels through the medium and produces along its path a series of ion pairs, until it is eventually stopped Photon *B* traverses the medium without being altered or deflected Photon *C* has acted just as photon *A*, knocking out a photoelectron, the *empty space in the K-orbit is immediately occupied by an electron from the L-orbit, and energy is released in the form of characteristic x-rays or photons* Photon *D* also strikes an electron of the *K*-ring, but loses only part of its energy in removal and acceleration of this electron, it is scattered in this process, and travels on in another direction and with reduced energy, until it experiences another secondary scattering absorption"

This diagram indicates how radiation (physical energy) is transformed into chemical energy through its capacity for altering the chemical characteristics of the atoms and molecules of tissue cells That is, it is now possible in many instances to explain the physiologic effects of therapeutic radiation in terms of familiar chemical reactions Of interest, nitrogen mustard is a radiomimetic drug in that the effects produced in the mammal are similar to those produced by x-ray (From GLASSER, O, QUIMBY, E H, TAYLOR, L S, AND WEATHERWAX, J L *Physical Foundations of Radiology*, Ed 2 New York, Paul B Hoeber, Inc, 1952)

To cite a second example, when acetylene is irradiated with radon a certain proportion of the molecules polymerize to solid cuprene Still again, when an homologous series of fatty acids is irradiated, it is found that the chief chemical reaction has been decarboxylation, as the length of the carbon chain increases, the proportion of radiochemical energy migrating to this one bon rises to a peak and then decreases

When amino acids are irradiated they ar quite specifically deaminated, nucleic acid are usually depolymerized

It is now possible, therefore, to describ many of the effects produced by radiation in common biochemical terms

Effects on Enzymes

Before closing this particular phase of the discussion, the effect of radiation on enzyme systems should be mentioned, since it is possible that the effects on enzyme systems may provide the amplification of primary biochemical effects necessary to achieve the clinical results commonly observed in human tissue. It has been found that in simple dilute enzyme systems the changes produced are quite similar to those for simple aqueous solutions, such as oxygen free water Under most conditions enzyme inactivation can be attributed to the products of the irradiation of water, an indirect effect [13] Of course, enzymes are not found in dilute pure solution in the living organism but even so, it is considered possible that labile enzymes are readily destroyed even in the presence of the usual complex cell constituents Should significant alteration of enzyme systems *in vivo* be demonstrated, the mutations in genes produced by radiation effects might be more readily explained

Radiation Effects on Microorganisms, on Cell and Chromosomal Structure, in Genetics, and in Carcinogenesis

Much work has been done concerning radiation effects at the cellular level and much is known in this area. However, as with the death of the living organism, the changes observed with the microscope are often hopelessly inadequate to explain cell death Thus, again, one must search for more subtle cytochemical changes or achieve further definition of cell alterations by use of such methods as the electron microscope. In other words, the usual microscopic studies of irradiated cells can reveal only a fraction of the picture which must be completed by sensitive studies of cellular physiology which are not necessarily reflected in visible alterations in cellular structure

It has been found that the physical and chemical consequences of the absorption of radiant energy by a cell occur in all parts of the cell irradiated but the final result of the radiation exposure varies both from one cell to another and indeed within the same cell As noted previously, the magnitude of the effect upon individual cells or upon individual components of the same cell has to do with the radiosensitivity of the particular type of cell and with the locus of the component within the cell A particular portion of a cell irradiated, such as the nucleus, may have potentialities for damage far in excess of other portions of the cell. In general, the portions of the cell having to do with fission are more sensitive to radiation than other portions and indeed various cells may be more sensitive to radiation in one or the other of the phases of cell division, namely, prophase, metaphase, anaphase, or telophase An extremely important effect of radiation is its effect upon chromosomes, an effect that can lead to actual physical breakdown. Breaks in chromosomes may be produced almost immediately, or potential breaks may be produced which may appear only after hours, days or weeks

GENETIC EFFECTS Susceptibility of chromosomes to radiation effects has, of course enormous import in the field of genetics Radiation damage to chromosomes may result in inhibition and cell death, but some cells may survive which carry chromosomal aberrations that are capable of producing permanent mutation. It is therefore not surprising that radiation has served as a particularly useful tool to geneticists, since by radiation one can achieve numerous mutations in a short period of time, to a point that such changes can be studied under a variety of circumstances Conversely, the mutations produced afford additional insight into the mode of action of ionizing radiation.

Two reports of special interest and importance have recently been made in this field both at the fiftieth anniversary symposium of the American Society of Biological Chemists. The first by Wendell M Stanley, was "Virus Composition and Structure—25 Years Ago and Now"[14] The second, by Norman H Horowitz, was entitled Progress in

Developing Chemical Concepts of Genetic Phenomena "[5] In the first of these reports the relationships between the phenomena of virus propagation, crystallization, and reconstitution were reviewed, with emphasis upon the basic importance of ribonucleic acid and desoxyribonucleic acid It was pointed out by Stanley that component parts of protein viruses may be separated for a prolonged period of time but that, if then brought together in correct proportions, they could reconstitute the virus which would then again cause the specific disease for which it was noted It was further found that the ribonucleic acid core of the virus contains the genetic message in causing disease by the reconstituted virus, and it is well known that nucleic acid metabolism is affected by irradiation

In developing further the theme that the genetic mutations may be explained on the basis of a chemical lesion, Horowitz noted that radiation produces mutations, apparently by knocking out a specific enzyme, that is, a single enzymic deficiency may be produced which permanently alters the chemistry of the cell Thus, a mutation could conceivably consist of a single biochemical lesion, and Horowitz offered the thought that the genetic message or set of instructions may consist of different arrangements of specific amino acids Pursuing the subject further, he pointed out that the subtle nature of certain mutations could be reflected in the fact that qualitative as well as quantitative changes in protein, perhaps of enzymes, might be produced For example, a protein substance may be rendered less stable to heat but similar to the parent protein substance (or enzyme) in all other respects The surgeon has an important interest in genetics, for the correction of malformations constitutes an important segment of surgical practice (p 629)

CARCINOGENESIS Since various forms of radiation can produce cancer—whether due to long-acting isotopes such as strontium, or radioiodine in the thyroid of certain rats, or chronic scars following radiation with x-ray, or by ultraviolet light in those exposed much to the sun—it is natural that radiation should be employed as a tool in the study of cancer and that such effects should be closely related to genetic disturbances and mutations For the cancer cell is a normal cell whose function has in some way been subtly altered to permit it to escape regulation by normal growth control mechanisms However, it is not necessary to discuss carcinogenesis at this point Suffice it to note that radiation is a mutagenic agent A number of chemical carcinogens have been found to be mutagenic, but not all mutagens are carcinogenic [13] (For another point of view, see p 173)

General Physiologic Effect in Mammals Including Man (Figs. 67 and 68)

Since irradiation affects the metabolism of nucleic acids, carbohydrates, fat, nitrogen, immunologic responses and the concentration and integrity of certain enzymes, it is to be expected that definite clinical effects are observed

The selective irradiation of certain organs such as the adrenals, spleen, or intestine produces unusually severe reactions in experimental animals Whole body irradiation, on the other hand, produces the so-called *radiation syndromes*, which may have particular emphasis in different areas The more well defined of these are the *hyperacute syndrome*, in which the dose of radiation is so great that death occurs very quickly from overwhelming ionization before the more subacute or chronic changes have occurred, the *intestinal syndrome*, which in the dog is associated with diarrhea, prostration, and bacteremia and which occurs approximately 5 to 7 days following the irradiation, and the bone marrow or *hematopoietic syndrome*, coming on after several weeks and characterized by anemia, leukopenia, spontaneous hemorrhage, and spontaneous bacteremia Years later malignant tumors and leukemia may appear

The usual course of events in *radiation sickness* due to severe exposure is one of

nausea and vomiting which usually begin within a few hours after the exposure, followed by a latent period relatively free of symptoms There may be considerable swelling of the part most immediately exposed Later nausea and vomiting may recur and diarrhea appears with blood in the stools mucous membranes become edematous There is apparently an increased capillary fragility and a circulating heparin like substance in the blood both of which result in hemorrhage into the tissues Dehydration and fever may follow and eventually there is a fall in blood pressure and death which usually occurs within 2 weeks

If the individual survives the early period changes in the peripheral blood and bone marrow begin to appear in several days, consisting chiefly of depression of the cellular elements as a result of necrotizing and antimitotic action of radiation on the hematopoietic tissues In addition blood loss and other ramifications of the altered physiologic balance contribute to the changes in the peripheral blood picture The abnormal bleeding which with depression of bone marrow elements results in the anemia is now considered to be due largely to thrombocytopenia However, the thrombocytopenia may be due to hemorrhage The bleeding which occurs into the tissues appears to be due as much to necrotic lesions and infection which secondarily involves the blood vessels as it is due to possible alterations in vascular permeability

The precise cause of death in the intestinal syndrome is obscure though it is felt that the diarrhea (with the water and salt loss which occurs) contributes to the lethal effects as well as perhaps an increased rate of entry of enteric organisms into the blood stream from a damaged bowel with resulting septicemia This bacterial invasion is also related of course to the diminished level of initial immunity and immunologic response but sepsis is not a major cause of death

Death may occur then from an overwhelming massive dose of radiation or from a somewhat smaller but still lethal dose causing depression of bone marrow elements and hemorrhage or from the particular involvement of the intestine in the form of the intestinal syndrome—all of which may begin to cause death in approximately 1 week reaching a peak in from 3 to 4 weeks

PROBABLE EFFECTS IN MAN OF VARIOUS AMOUNTS OF ACUTE PENETRATING RADIATION (FROM EFFECTS OF ATOMIC WEAPONS 1950 p 342)

Acute Dose	Probable Early Effect
0–25 r	No obvious injury
25–50	Possible blood changes but no obvious injury
50–100	Blood-cell changes some injury no disability
100–200	Injury possible disability
200–400	Injury and disability certain death possible
400	Fatal to 50%
600 or more	Fatal

Fig 67 These estimations have been fairly well sustained by subsequent data obtained from accidentally irradiated subjects (From SPARROW A H, AND RUBIN B A In *Survey of Biological Progress* Vol. II New York Academic Press, Inc 1952)

APPROXIMATE LD_{50} FOR VARIOUS MAMMALS RESULTS ARE FOR TOTAL BODY IRRADIATION USING 200 KVP X RAYS

Organism	Approximate LD^{50}
Guinea pig	200 r
Dog	300 r
Mouse	400 r
Mouse LAF	600 r
Monkey*	500 r
Rat	590 r
Rabbit	790 r
Man	400 r

From Tabulation of available data relative to radiation biology NEPA 1949 except for man

* 250 KVP x rays

Approximation only

Fig 68 X-ray tolerance differences among mammals (From SPARROW A H, AND RUBIN B A In *Survey of Biological Progress* Vol. II New York Academic Press, Inc 1952)

and then exhibiting a gradual decline However, if the individual survives this period certain other findings may appear, as in the Japanese at Hiroshima The more delayed effects are the formation of keloids, cataracts, insidious and chronic anemia, and some sterility and amenorrhea It is as yet too early to determine whether additional cancers and leukemia, as well as late mutations, will be noted, but these are not unanticipated

In concluding this survey of the more important effects of radiation in mammals, the matter of *physiologic balance* should be mentioned It is well known that irradiation of one part of the organism may result in altered function of other parts of the organism It is not settled whether such effects on distant parts arise from toxic materials formed in the irradiated part or, conversely, whether observed phenomena are a reflection of an effort of distant organs to come to the assistance of the damaged tissues by minimizing the radiation effects That healthy tissues with normal function can diminish the effects of ionizing radiation has been shown by means of parabiosis (p 116) Irradiated animals joined to a normal animal exhibit a greater tolerance for lethal irradiation than do animals who are not joined to a normal animal, emphasizing that the effects of radiation are complex and are modified by many different factors

Protection Against Ionizing Radiation Injury

The mechanisms of radiation protection have to do also with problems of radiosensitivity It has been indicated previously that the nucleus is more sensitive to radiation damage than is the cytoplasm, though secondary effects upon the nucleus can occur from injury to the cytoplasm As pointed out by Patt,[11] an indication of the importance of metabolism in its broadest sense may be the fact that the cell in mitosis is usually more susceptible to injury than is the cell at rest Again, even in mitosis there are differences, for cells in the prophase or metaphase are generally the most sensitive to radiation injury Curiously, the degenerative changes are likely to occur at the time of cell division regardless of when the cell was irradiated, this suggests fundamental physiologic changes which only later become apparent microscopically The fact that physiologically inactive or dormant cells usually suffer less damage than do their active sister cells suggests enzymic rôles, in that certain of these may be inactivated by radiation This further emphasizes that, since most if not all cellular activities are controlled by the nucleus, radiation damage to the nucleus would be expected to produce important physiologic effects[13] The marked variations in sensitivity of different tissues to ionizing radiation, however, is not always readily explained In Table 9 are given the relative sensitivities of different human tissues to radiation

The Modification of Radiobiologic Effect In Simple Systems

From the point of view of protection of mammals from radiation injury, it is of interest to know what factors may diminish the effects of ionizing radiation In contrast, in treating cancer one may be interested in potentiating or amplifying the effects of ionizing radiation, and such studies have engaged a number of investigators in recent years

It has been shown that the exclusion of water and of oxygen, as well as the lowering of body temperature, all tend to diminish the effects of ionizing radiation upon simple systems This is because the exclusion of water tends to reduce the indirect effects of radiation While it is not the purpose here to describe in detail specific factors which may protect against the effects of radiation, several measures should be listed These are the use of reducing compounds, desiccation of the substance to be irradiated, lowering the temperature of the target material, diminishing the blood supply to the part (which probably protects by reducing the oxygen supply), and the addi-

tion to the irradiated solution of an agent such as glutathione which afford protection of —SH enzymes that would otherwise be oxidized by the oxidants formed in the aqueous solution Cysteine and a number of other compounds have been found to afford some protection against various effects of irradiation The protection effect by sulfhydryl compounds is characterized by a change in the slope of survival curves of *Escherichia coli* or other preparations subjected to radiation injury Cysteine has been shown to protect rats and mice against acute lethality, as have glutathione and British anti lewisite (BAL) However, to be effective these substances must be given prior to irradiation.

To summarize, it has been demonstrated that certain reducing agents are effective in protecting some animals against ionizing radiation, and this again emphasizes the oxidative nature of the chemical effect involved in the production of biologic damage Protection of the —SH group during radiation has been shown to permit later regeneration of enzyme activity

MORE GENERAL PROTECTIVE MEASURES In mice particularly, it has been shown that shielding of the spleen affords considerable protection against radiation injury, presumably because of its hematopoietic functions. Of course, for many years the radiologists have protected with appropriate shielding the organs which they did not wish to irradiate Transfusions tend to diminish the effects of erythropenia and leukopenia, and to offset the hemorrhagic tendencies which follow exposure to ionizing radiation Head shielding affords much protection in dogs

Liberal doses of antibiotics limit the infection which develops in the irradiated animal It was found that Aureomycin may diminish the diarrhea in rats that follows irradiation life was prolonged for from 5 to 7 days at which time the animals then began to die with signs of hemorrhage [10]

Unfortunately animal studies (Fig. 69) cannot be projected to man without qualification, for there is much variation in species resistance to irradiation For example while the approximate LD_{50} for total body irradiation using 200 KVP x rays is 200 r (roentgen units) for the guinea pig, the dosage varies considerably in other animals and is approximately 400 r in man [13]

Finally it scarcely need be said that the effects of radiation *per se* are by no means well defined and the more chronic effects, especially, are just beginning to be appreciated It has been found that physicists exposed to chronic but small dose irradiation have gradually developed cataracts, and leukemia is known to be more prevalent among radiologists than among other physicians or among the population at large The relative sensitivities of different organs are shown in Table 9, as indicated previously

No effective *treatment* for massive radiation exposure exists at present.

Radiation Dosage Units

One of the particular difficulties in studying the effects of radiation upon living systems has been the wide dosage range used by different investigators and, all too frequently, the lack of scrupulous attention to the careful measurement of the dosage used to achieve particular effects It is readily apparent that we must have some measurement of radiation dosage units that can be uniformly applied in treating patients For this reason, a radiation therapy unit should be carefully standardized and calibrated by a radiation physicist before permission can be obtained for using it clinically

What is then, the common unit of measurement of radiation? Much has been said regarding ionization, and it is this effect that is measured in determining the strength of a particular energy source The reason for this is that the energy absorption by a biologic system in the usual radiation experiment is only sufficient to raise its temperature about 0 1 C, rendering measurement of temperature inadequate for careful calibration.[13] Furthermore, since it is difficult to measure ionization in a biologic sys-

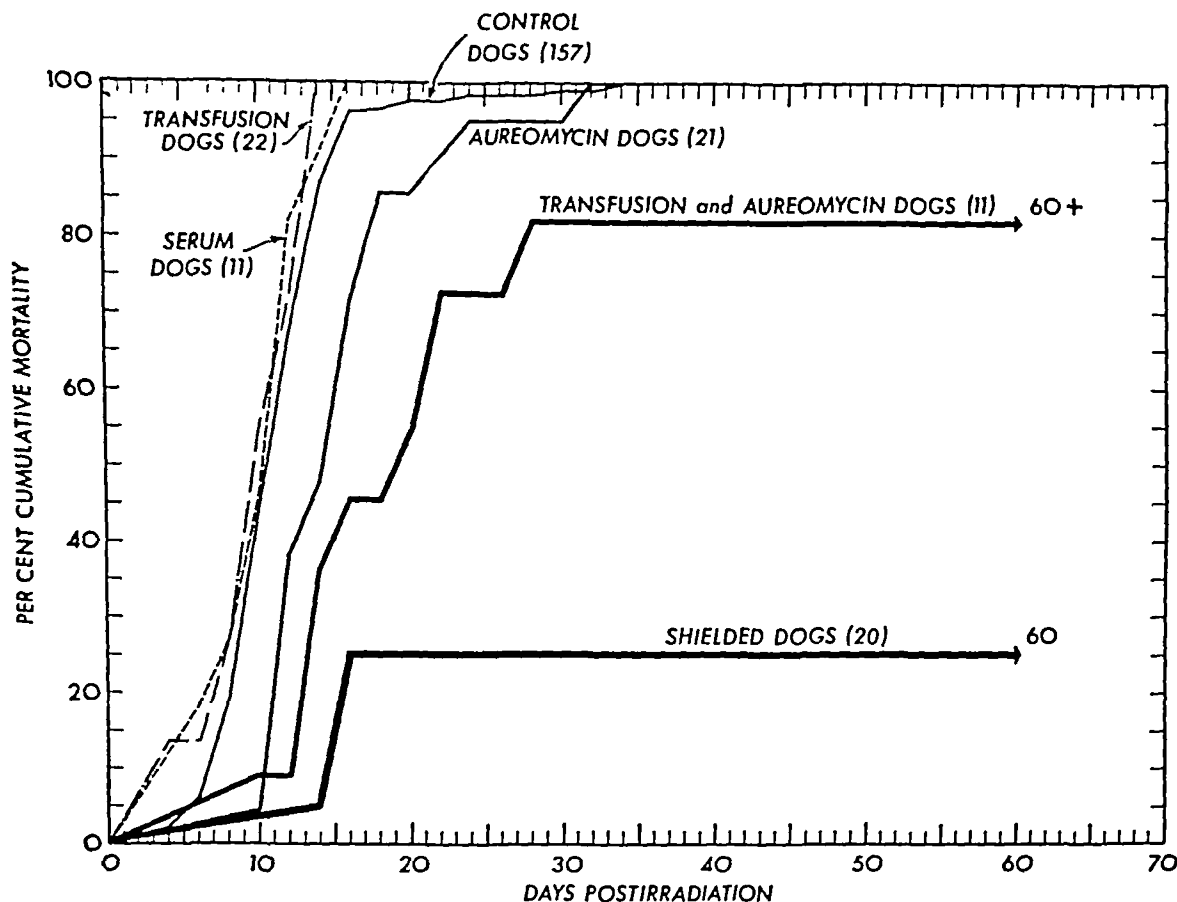


Fig 69 Failure of antibiotics and/or transfusion to reduce significantly the mortality in radiation injury Cumulative mortality curves of dogs subjected to various types of post-radiation treatment Included for comparison are the data obtained from head-shielding The 450 r x-ray exposure is about 100 r above the LD_{100} for this laboratory (From ALLEN, J G In *Surgery—Principles and Practice*, edited by Allen, J G, Harkins, H N, Moyer, C A and Rhodes, J G Philadelphia, J B Lippincott Company, 1957)

tem, in practice irradiation dosage (in "r" or roentgen units) is determined from the ionization produced in some measured gas volume, usually air Even so, it is generally agreed that this type of measurement is only relatively accurate When the energy lost in tissue is equal to that lost in air by 1 r, the dose is spoken of as 1 roentgen-equivalent-physical (1 rep) This unit is applied to charged and uncharged particle radiations, as well as to x-rays and gamma rays [13]

Other Clinical Considerations in Regard to Radiation Therapy

WOUND HEALING FOLLOWING IRRADIATION OF THE TISSUE It is a common impression that an incision made through skin that has been irradiated will not readily heal However, in experimental studies in rats Lawrence, Nickson, and Warshaw[7] found that standard abdominal incisions made at various times after irradiation of the wound areas healed satisfactorily, though perhaps not quite so rapidly as in animals who had not been irradiated The final wound strength was equal to that in the control or nonirradiated animals It was their conclusion that there was no practical advantage in delaying surgery more than 3 weeks after irradiation Of interest was the fact that the presence or absence of irradiation-induced skin erythema, *per se*, seemed to have little effect on the rate of wound healing In a different type of study, Gustafson and Cebul[2] found that the resection of a segment of ileum was well tolerated in dogs receiving 200 or 300 r of whole body irradiation 20 hours prior to surgery The surgical wounds

TABLE 9 CLASSIFICATION OF MALIGNANT TUMORS IN RELATION TO RADIATION TREATMENT

I Sensitive tumors
- A Embryonal origin
  - Seminoma
  - True embryonal tumor of ovary
  - Other embryonal tumors e g Wilms
- B Reticuloendothelial origin
  - Lymphosarcoma
  - Reticulosarcoma
  - Thymoma
  - Some endotheliomas
  - Ewing s tumor
  - Hodgkin s disease
  - The leukemias
- C Neuroblastomas

II Tumors of limited sensitivity in accessible sites
- Carcinoma of the mouth including tongue and lip
- Carcinoma of the skin of face and hands and elsewhere
- Carcinoma of the cervix uteri
- Carcinoma of the vagina
- Carcinoma of the anus—if of limited size
- Carcinoma of the bladder—if of limited size
- Carcinoma of the maxillary antrum
- Intrinsic carcinoma of the larynx—if limited to the cord
- Retinal glioma
- Carcinoma of the breast and in lymph nodes
- Mixed tumors of the parotid
- Benign giant cell tumor of bone

III Tumors in which radiotherapy has a low cure value but a definite palliation value
- Carcinoma of kidney (hypernephroma)
- Carcinoma of ovary (except embryonal)
- Cerebral tumors
- Carcinoma of bladder or larynx—unless limited (see above)
- Thyroid tumors
- Salivary gland tumors (other than parotid)
- Carcinoma of esophagus
- Carcinoma of lung
- Isolated bone metastases
- Malignant mediastinal tumors

IV Tumors where radiotherapy is rarely of value
- Osteogenic sarcoma
- Fibrosarcoma
- Other resistant sarcomas (myosarcoma liposarcoma etc)
- Melanoma
- Carcinoma of stomach or gut
- Metastases in liver or lung
- Carcinoma of prostate

TABLE 9 —Cont d

* Modified from RALSTON 1 *The Treatment of Malignant Disease by Radium and X rays* London Edward Arnold & Co 1918

of the abdomen healed well in the operated dogs, and wound infection did not occur in those dogs having subcuticular skin closures The most common pathologic finding in dogs dying following irradiation was a profound bacterial pneumonitis

Despite these reports, however, we are still somewhat reluctant to operate through recently irradiated tissue

RADIATION INJURY TO THE SMALL AND LARGE BOWEL. It is not particularly uncommon to detect irradiation effects upon the small and large bowel following treatment of uterine cancer with irradiation (Fig 70) The rectum being in closest proximity is the structure most frequently damaged, though injuries to the bladder ureters and small intestine may also be encountered When the small bowel is damaged by radiation intestinal obstruction is the usual complication which brings the patient back for further treatment Perforations or ulcerations in the small intestine as the result of radiation injury are rare Instances of serious hemorrhage and bloody diarrhea from the colon may develop

In contrast to the more severe effects of hemorrhage and perforation, immediate though temporary effects of irradiation on the intestine are not unusual beginning



Fig 70 Postirradiation fistula between right iliac artery and terminal ileum This woman had been treated for cancer of the uterus by both radical surgery and irradiation She was brought to the hospital weeks later with massive bleeding from the sigmoid colostomy The lesion shown was excised (artery ligated) with complete recovery

during the course of treatment and often subsiding several weeks following its cessation The most common findings are nausea, diarrhea, abdominal cramps, and edema and hyperemia of the intestinal mucosa

The *treatment* of the more severe complications, consisting of hemorrhage or perforation, is the same as were these complications caused by any other type of injury Resection of the involved bowel or closure of perforations is indicated

POSTRADIATION FIBROSIS OF THE LUNG This is a chronic condition of the lung which is most often caused, not by irradiation of cancer of the lung itself, but by irradiation for carcinoma of the breast This results in fibrosis of the ipsilateral lung with, not infrequently, an harassing cough and, occasionally, hemoptysis These symptoms may be distressing enough but, if sufficient pulmonary tissue has been irradiated, the fibrosis may be so extensive as to result in serious dyspnea There has been an increasing tendency in recent years to resect the most diseased portion of the lung, if this is not too extensive

DEVELOPMENT OF CANCER IN IRRADIATED AREAS It is a relatively rare complication in modern times, but formerly the removal of hair and other "cosmetic" uses of radiation resulted in the development of carcinoma of the skin Many physicians develop skin cancer involving the hands as a result of careless exposure in the use of x-ray, especially at fluoroscopy

Medical Uses of Isotopes: Research, Diagnosis and Therapy

HISTORICAL COMMENT The present widespread use of isotopes had its inception in isolated studies many years ago Following the discovery and separation of pure radium by Marie and Pierre Curie in 1902, physicists everywhere became extremely interested in obtaining radioactive substances in a pure state However, by chemical means this proved exceedingly difficult to achieve in many instances Failure on the part of competent physicists to separate such substances led to the concept of "chemically practically identical elements" That is, while by physical means it might be possible to separate the radioactive substance from a nonradioactive substance of similar composition, the tissues of the body could not distinguish one from the other in utilizing them in cellular metabolism This gave rise to the concept of "isotopy," somewhat the result of the formulation of "displacement laws" of atomic structure, which concept was introduced in 1913 [3] At about this time von Hevesy, having journeyed from the laboratory of Lord Ernest Rutherford in England to the Institute for Radium Research of the Academy of Sciences in Vienna, actually accomplished the initial use of chemically practically identical elements as indicators Concluding that, if radium D could not be separated from lead, it should be possible to label lead by adding to a known amount of lead chloride radium D chloride prepared from old radium emanation tubes, von Hevesy and his associate, F A Paneth, utilized this fact to use labeled lead and labeled bismuth as indicators in the field of inorganic chemistry and physical chemistry in 1912 and 1913 [3] However, it was not until approximately 10 years later, in the laboratory of Niels Bohr at the Institute in the University of Copenhagen, that radioactive indicators were used in the study of the living organism, the uptake of lead by plants and the distribution of lead and bismuth in the animal organism were investigated

Von Hevesy further recalls[3] that the application of lead salts in cancer therapy was first suggested by Blair Bell of Liverpool in the latter portion of the twenties, and von Hevesy undertook to study the distribution of lead between normal and cancerous tissue, using radium D as a tracer It was during the course of this work, performed in the University of Freiberg in Germany, that he asked the pathologist Aschoff to delegate one of his assistants to participate in this research Among the persons Aschoff designated was, later in the studies, his chief chemist, Rudolf Schoenheimer Although the

s of investigations gave a negative re- as cancerous tissue accumulated ap- imately the same amount of lead as nor tissue, the cross fertilization between enheimer and von Hevesy resulted in former's becoming acquainted with the of isotopic indicators This had a far ing influence in the field of intermedi metabolism for during the 1930 s, now e United States, Schoenheimer, in col ration with David Rittenberg per ed some of the most brilliant tracer es conceived up to that time At that y date, they demonstrated a continuous wal of the molecules of fats and proteins e animal organism and actually deter d the speed of many of these processes s work was published in a monograph tled *The Dynamic State of Body Con ents* which did much to reorient scien thought with respect to the processes of rmediary metabolism.

ollowing the discovery of heavy hydro (deuterium) by Urey in 1932, an isotope ch is not radioactive but is a stable ' ope, further application of the isotopic mic was made possible The first applica of deuterium as a tracer was the study he rate of interaction between the water ecules of the goldfish with those of the ounding water Rapid exchange occurred vertheless the extent of intrusion of deu um into the fish could only be explained assuming a rapid interchange of a part of hydrogen atoms present in the organic lecules of the fish with those of the water lowing this von Hevesy and Hofer[4] per med their classic determination of the to body water content of a human being and the mean half time of water molecules in human body This was carried out by ing the individual drink water containing nown amount of heavy water and then de- mining the rate of heavy water excretion the urine. This study was subsequently lely confirmed (p 28) The time the av ge molecule of water remains in the body the normal individual who does not have essive rates of water turnover due to fe- le illness or other cause is from 9 to 13 days, with an average of approximately 11 days Most of the heavy water is excreted by the end of approximately 30 days There is a radioactive isotope of hydrogen, ultra heavy hydrogen or tritium (mass 3), which is also available for use in tracer studies of water metabolism

In concluding his survey of some of the historic milestones in the development of the now commonplace use of radioactive in dicators, von Hevesy singled out the dis covery of the production of artificial radio activity by Joliot and Madame Joliot Curie as one of the truly great advances in the field. This opened the way to the applica tion of radioisotopes of almost all common elements as indicators, since almost any element desired could be artificially ren dered radioactive and thus used as a tracer for metabolism in the body and throughout the biologic world The preparation of such material was, of course, enormously speeded up by the development of the cyclotron by Ernest Lawrence

Use of Isotopes in Research

The use of isotopes is so routine in in vestigative work throughout all branches of science that it is impossible to survey, even were it desirable, even a portion of such usage Rather, we shall complete this par ticular phase of the discussion by mention ing only a few examples Isotopes of hydro- gen have been mentioned Prior to the availability of isotopes which could readily be used in human beings, it was possible to determine the metabolic fate of for exam ple nitrogen compounds only by balanc studies That is one measured the intake c nitrogenous materials and measured the ex cretion of nitrogen in the urine and feces I was considered that when the intake ex ceeded the output the patient was in ' posi tive nitrogen balance whereas when th output exceeded the intake he was in 'nega tive ' balance The same type of balanc studies were applied to many other organi and mineral constituents of the usual food stuffs However while this permitted

inference as to what was taking place with respect to the breakdown and utilization of the nitrogenous products ingested, it offered virtually no specific information regarding the metabolic pathways which this ingested nitrogen might have taken before being finally excreted as urea With the advent of tracer substances of nitrogen, hydrogen, carbon, phosphorus and other elements, it became possible to identify in the urine, feces, blood, and tissues intermediary products of the original substance ingested It was shown, for example, that there is a continuous turnover of fatty acids, that glucose can indeed be formed from fatty acids (which had been debated for many years), and that, in general, complex compounds in the body are actually built from basic and relatively simple structural units That is, the body preferentially uses small building units or short chain compounds to achieve even the more complex molecules, rather than stamping the complex molecules out of an even more complex precursor [8]

TABLE 10 Surgical Uses of Isotopes Some Examples

- I Diagnosis
  - A Radioiodine in hyperthyroidism
  - B Radiophosphorus in localization of brain tumors
  - C Thorotrast in identifying liver abscesses and metastases
  - D Radioactive serum albumin (RISA) for measurement of plasma volume
  - E Radioactive iron for detecting diminished life span of red cell
- II Therapy
  - A Radioiodine in hyperthyroidism and in thyroid cancer
  - B Radiophosphorus in polycythemia vera and metastatic solid tumors
  - C Radiogold for ascites or pleural effusion
- III Research
  - A D_2O (heavy water) for the measurement of total body water
  - B *Radiosodium and radiopotassium* for the measurement of the body pools of these ions
  - C Radiosodium for a great variety of circulatory "clearance," cardiac output and related studies
  - D Radioiodine for investigation of iodine metabolism
  - E Radiocarbon for metabolic investigations

It will thus be seen that the use of isotopes has greatly extended the range and precision of information achieved with the balance study, and such studies have in many instances demonstrated that previous concepts were erroneous

Innumerable other examples could be cited but there will be mentioned only the use of stable and radioactive isotopes in measuring body water, extracellular water, plasma volume, red cell mass, length of life of the red cell, the uptake of radioiron by bone marrow in the production of red cells, radiosodium in the measurement of exchangeable sodium, radiopotassium in the measurement of exchangeable potassium, and the use of strontium and other elements in demonstrating a surprisingly rapid turnover in the mineral content and metabolic processes of bone itself Until isotopes became available, bone was often considered a very static structure, a concept which has been demonstrated to be quite untenable, for bone too is in a state of constant molecular change Radioactive calcium and radioactive gallium have also been particularly useful in the study of bone metabolism, since they, with strontium, are rapidly taken up by bones

Diagnostic Uses of Isotopes (Table 10)

THE IMPORTANCE OF "HALF-LIFE" IN HUMAN APPLICATION The applicability of radioisotopes in human beings has to do both with the amount of material that must be injected to permit subsequent detection in body tissues, fluids, or excreta, and with the length of time the element is reasonably radioactive, *i e*, its half-life Heavy hydrogen (deuterium), usually in the form of heavy water (deuterium oxide), is a stable isotope and is not radioactive A radioactive isotope differs from one which is not radioactive only in the composition of the atomic nucleus usually because of an extra neutron The additional neutron does not affect the chemical properties of the atom sufficiently to

enable living organisms to differentiate the isotope from its natural counterpart, in the course of usual metabolic processes. To be sure, the isotopes of hydrogen exhibit differences in rates of diffusion throughout a solution, but diluted isotopes can still be used satisfactorily for tracer work in metabolic studies despite such minor differences in physical properties.

The concept of half life. As noted, there are differences between stable or nonradioactive isotopes and radioactive isotopes. The radioactive isotopes are in a constant state of decomposition and the rate of this decomposition is referred to as the *half life*. In Table 11 it is seen that whereas the half-life of iodine is only 8 days, the half life of chlorine is more than a million years. The half lives of other isotopes commonly used in research and therapy lie between the extremes, most of them much nearer the half life of iodine. That of sodium is quite short, being 14.8 hours. The *half life* is not to be confused with the *biologic half time*. The latter refers to the average length of time that a number of simultaneously ingested atoms will remain in the body.

The rate of breakdown or disintegration of the nucleus of radioactive atoms is a measure of the nuclear stability of the isotope and can be measured for purposes of determining the half life. Naturally, isotopes with a relatively short half life are safer for clinical use, since the dose of irradiation is limited regardless of the persistence of the element in the body. For example, if a certain amount of radioactive sodium were to be introduced into the body, in 14.8 hours only one-half of the original radioactivity in the sodium would remain, in 29.6 hours only one fourth, in 44.8 hours, only one-eighth, etc. In contrast, the radioactivity in a given amount of radioactive carbon would be unaffected by even 1 year or 10 years or 20 years since, as seen in Table 11, the half life of radiocarbon is 5568 years. Obviously, were the carbon given to the living organism never excreted, a tremendous amount of radiation would occur over the

TABLE 11. HALF LIVES OF COMMONLY USED ISOTOPES (APPROXIMATE VALUES)

Isotopes	Half Life
Calcium[45]	163 days
Carbon[14]	5508 years
Chlorine[36]	3.08 × 10^5 years
Cobalt[60]	5.27 years
Gold[198]	2.7 days
Iodine[131]	8.08 days
Iron[59]	45.1 days
Phosphorus[32]	14.3 days
Potassium[42]	12.44 hours
Sodium[24]	14.8 hours
Strontium[89]	53 days
Strontium[90]	25 years
Yttrium[91]	60.5 days
Tritium	12.46 years

life span of the organism. The fact is, however, that very minute amounts of carbon can be used in human metabolic studies. Since the amount introduced is quite small and since carbon is in a state of constant turnover and excretion, the injected radioactive material would also be turned over and a portion regularly excreted until eventually the amount in the body could scarcely be detected. Nevertheless, it is properly the short half life compounds such as phosphorus, sodium, potassium, and iodine that have been most extensively used in human study and therapy. Radioactive iron, with a half life of about 45 days, has also been used for the study of rates of red cell formation and destruction and for the determination of red cell mass, but chromium has largely replaced iron for most such measurements.

RADIATIONS EMITTED BY VARIOUS RADIOACTIVE ISOTOPES. When the radioactive atom disintegrates, the molecule carrying it is shattered and beta, gamma, or less frequently alpha and neutron types of emanations are emitted from the nucleus.[9] As has been seen, alpha particles are heavy, doubly charged particles composed of two neutrons and two protons and are identical with the nucleus of the helium atom; they result in intense but localized damage. Beta particles are electrons with a penetrating power up to

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8 mm in tissue, but their effects are primarily restricted to the immediate vicinity of the disintegration. Gamma rays, similar to x-rays, can penetrate for many centimeters, influencing the intermediate tissues. Radioisotopes which emit gamma radiation are much more hazardous to work with than are those which emit alpha and beta particles. Finally, neutrons, lacking an electrical charge, also penetrate deeply but produce local defects along the tract.

DIAGNOSTIC USAGE OF RADIOACTIVE IODINE. Radioactive iodine has been proved to be by far the most useful isotope thus far. The avidity of the thyroid for iodine has made it possible to determine thyroid activity by measuring the rate of uptake of radioiodine. In brief, the patient ingests a measured amount of radioactive iodine, usually 100 to 200 μc., in water. Twenty-four hours later a scintillation counter is placed over the thyroid gland and the proportion of the ingested dose in the thyroid is estimated, due correction being made for decomposition or decay of the ingested iodine, that is, for the natural decline in the specific radioactivity. The uptakes in euthyroid, hyperthyroid, and hypothyroid individuals have been indicated elsewhere (Fig. 225). Initially, the amount of iodine excreted in the urine was used as an indirect measure of thyroid activity, but more recently the excretion in the urine has been abandoned because of the greater simplicity of merely measuring the uptake by the thyroid gland itself. The microcurie (μc.) is 1/1000th of a millicurie (mc.) or 1/1,000,000th of a curie. The millicurie is defined as the amount of the isotope giving 2.2×10^9 disintegrations per minute. It is roughly equivalent to the number of disintegrations occurring in 1 mg. of radium.[13]

To give an indication of the range of dosages of radioiodine used for different purposes: whereas from 100 to 300 *microcuries* of radioiodine may be given the patient for the purely diagnostic and nontherapeutic study of thyroid activity, from 5 to 15 or more *millicuries* will usually be required for the successful treatment of hyperthyroidism. For the eradication of thyroid activity in thyroid cancer, as much as 30 millicuries may be used. Such high dosages have also been used to produce "medical thyroidectomy" in patients with heart disease.

USE OF RADIOACTIVE PHOSPHORUS IN LOCALIZATION OF BRAIN TUMORS. Only one additional use of radioisotopes in diagnosis will be mentioned, and this is the use of radioactive phosphorus in localizing brain tumors.[9] The concentration of injected radiophosphorus in neoplastic tissue may be perhaps five times that of the surrounding normal tissue. Whereas the isotope cannot be used effectively in the actual irradiation of such tumors, it can be useful in the localization of a tumor at the time of craniotomy when its location and extent are not clearly apparent. This is done by probing the brain in the suspected areas with a small scintillation probe that is approximately 2 mm. in diameter and which is superior t the Geiger probe.

Use of Isotopes in Therapy

The therapeutic use of isotopes is still i its infancy, and the indications are changin so rapidly that it is not practicable to b too dogmatic. Nevertheless, the therapeuti use of certain isotopes is already well estab lished. The use of radioiodine in the treat ment of hyperthyroidism and in thyroi cancer has been mentioned. The high con centration of radioactive phosphorus, a strong beta emitter, in bone and bone mar row has permitted the successful use of thi isotope in the treatment of polycythemia vera. A single dose may result in a remission lasting from 6 to 12 months. The isotopic treatment of leukemia has been rather less successful. Radiophosphorus has also been employed in the treatment of certain solid tumors.

The *radioactive cobalt unit* is now widely utilized as a powerful source of gamma irradiation for deep therapy in the management of malignant tumors. This cobalt "bomb" has the great advantage of being a

relatively inexpensive means of achieving deep radiation therapy, as compared with the more expensive high energy x ray unit It is obtained from the pile at Oak Ridge The effective life of the unit is approximately 5 years after which the radioactive unit can be replaced

Radioactive gold has been introduced into body cavities particularly the thorax, in which malignant disease was diagnosed. It has also been injected directly into a tumor mass for local irradiation According to Kelsey,[6] 99 per cent of the gold introduced is permanently fixed at the site of injection Since the half life of Au^{198} is 2 7 days and that of Au^{199} is 2 3 days, the radiation continues for a maximum of only 2 to 3 weeks after fixation While the results in treating malignant tumors of the pleural cavity (often metastatic tumor) with radiogold have not been spectacular, the pleural effusion is frequently diminished and some improvement is realized

Certain skin lesions may be treated by applying radioactive isotopes directly over the lesion Finally there is the recently introduced technic of, at operation introducing coils of polyethylene tubing through and through the tumor as for example a carcinoma of the pancreas and then bringing both ends of the polyethylene tubing out through the abdominal or other incision The radioactive isotope can then be introduced and placed in the portion of the polyethylene tubing that is within the cancer effecting local irradiation of a tumor that could not be readily treated with irradiation from an external source

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Chapter 9

Surgical Enzymology—The Importance of Enzymes and Their Use in Diagnosis and Treatment

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Rôle of Enzymes in Biochemistry

Throughout the preceding chapters frequent reference has been made to enzymes Most of the chemical processes which constitute life itself are catalyzed, and the overwhelming majority of catalysts are enzymes This being the case, the importance of enzymes in human physiology becomes apparent, and the study of enzymes and their functions now constitutes a major field in biochemical research The known enzymes number in the dozens, and will later perhaps number in the hundreds Many disease processes have proved to be due to a specific enzymic deficiency or "enzymic lesion," and many others are suspected to be due to such lesions

The rôle of adrenocortical, thyroidal, and other hormones in promoting successful resistance to various forms of stress has long been considered to be mediated through enzyme systems with their subsequent effects upon cellular biochemistry It was seen in the section on cancer that perhaps the single most characteristic biochemical lesion in malignancy is a diminished liver catalase activity in the presence of a rapidly growing tumor This of course strongly suggests that enzymic processes are deranged and that they may have to do with carcinogenesis Earlier, mention was made of the data which serve as evidence for the development of a biochemical basis for genetic phenomena Horowitz[10] has suggested that each enzyme may be controlled by a specific gene wh results in the transfer of a single spec biochemical function In support of such hypothesis, there are definite heredit diseases that are caused by the absence a single specific enzyme (*e g* , alkaptonuri It has been seen that radiation-induced m tations may consist of the absence of a sin specific enzyme, with a resulting speci biochemical abnormality in the muta strain In other words, there is a considera body of evidence being marshaled to su port the view that the characteristics of t father and mother are transferred to t children in a random combination of gen that each gene controls a specific enzym messenger, perhaps consisting of a partic lar arrangement of amino acids, and th this results in a particular characteristic i the progeny that is given expression throug a particular chemical reaction [10]

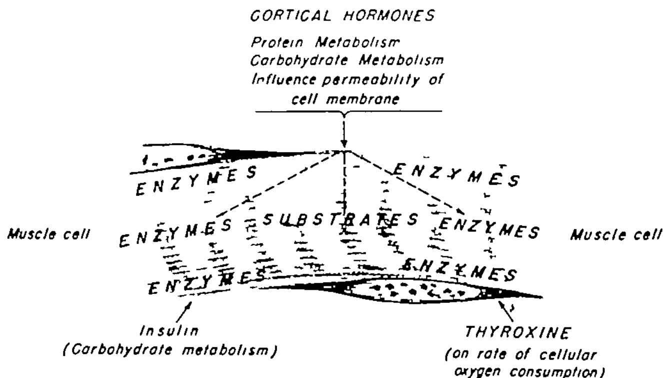
EVIDENCE THAT ENZYMES ARE CONTROLLE BY HORMONES It has been intimated abov that the rôle of hormones in stress is medi ated through enzymes, with a consequen effect upon cellular chemical processes Al though the evidence for this is by no mean complete—and may even be considered a somewhat tenuous—a basis for this assump tion was suggested by the Cori's, in that th activity of hexokinase, which catalyzes a essential intermediate step in the oxidatio of glucose to water and carbon dioxide, i controlled by insulin and by a pituitary an-

tagonist.[4] If hexokinase cannot act, glucose is not utilized normally and the manifestations of diabetes mellitus appear This has stimulated interest in the use of fructose in diabetes mellitus, since hexokinase is not required for the phosphorylation of this substance and thus there appears to be no block in this reaction in diabetes [16]

Other examples of the role of hormones in the regulation of enzymic activity could be cited. To give one more cytochrome *C* is an important respiratory enzyme concerned with the cellular utilization of oxygen Drabkin[5] showed that the tissue concentration of this enzyme could be reduced by thyroidectomy or by the administration of thiouracil

THE NATURE OF ENZYMES AND THEIR IMPLICATION IN SPECIFIC DISEASE STATES * As enzymes are organic catalysts, they alter the speed of their respective chemical reactions without appearing in the final product of the reaction Tagnon[22] offers as an example the fact that colloidal platinum, a simple catalyst, catalyzes the decomposition of hydrogen peroxide into water and oxygen A catalyst does not of course create a chemical reaction it merely regulates the rates of previously present reactions Enzymes differ from some other catalysts, however, in that each enzyme catalyzes one kind of reaction only Most if not all of the enzymes known are protein in nature with a relatively high molecular weight, are inactivated by heat, and can generally be extracted from the cells in which they are produced In this connection, one might note that enzymes are usually intracellular and that most of them function in the cytoplasm of the cell (Fig. 71)

To implicate enzymes as specific etiologic agents in disease, additional examples may be given The rôle of hexokinase in the genesis of diabetes mellitus was described The abnormality of albinism, in which phenyl alanine is not converted to melanin, repre-



Possible Site of Action of Hormones

Fig 71 If the prevailing belief that hormones exert their manifold effects by influencing enzyme activity is a valid one, then the question arises as to the point at which such influence is effected (From HARDY J D *Surgery and the Endocrine System* Philadelphia W B Saunders Company 1952)

sents an enzyme deficiency Pancreatitis represents an often fatal inflammatory process in the pathogenesis of which enzymes surely play an important rôle, whether because of their activation or because of the absence of a normally present inhibitor from the blood[11] Alkaptonuria, in which the excreted homogentisic acid causes the urine to turn black on standing, is another example Phenylketonuria, in which phenylalanine metabolism is deranged and a mentally defective person results, is still another example of an abnormal gene's producing abnormal enzymic activity

This brief list of illustrations might be concluded by noting that the biochemical *identity of the cells of the different organs of the body is likely to result from the nature and proportion of the enzymes contained in the various cells* In passing, it will be perceived that the morbid microscopic observations of the pathologist cannot, alone, presume to explain the chemical pathology of disease the subtle biochemical disturbances which threaten or even destroy *life may often have taken their toll without* producing visible anatomic changes However, there is reason to believe that with the tremendously increased resolving power of the electron microscope the altered biochemistry which can frequently be demonstrated in disease states can be correlated with definite alterations in the finer details of the structure of both the cell nucleus and the cytoplasm Of course, pathologists themselves are keenly aware of the limitations of gross and microscopic observation, and the pathologists in our hospital now report in two categories first, gross and microscopic findings and, second, the probable biochemical and physiologic derangements that existed during life

ENZYME INHIBITORS Since *a highly developed system of checks and balances exists in the body with respect to most biochemical phenomena,* it would be surprising indeed if such a regulating scheme were not present for enzymes, and such does exist For example, a rise in serum hyaluronidase inhibitor usually follows the wounding of an animal Further, the mechanism involved in anaphylactic shock and other allergic phenomena is thought to be enzymic in nature, the general consensus is that histamine is liberated through the activation of proteolytic enzymes and that this histamine then prevents other enzymes from functioning normally This hypothesis stimulated the search for substances similar in structure to histamine which would act as histamine antagonists in allergy states, and compounds such as Benadryl and Pyribenzamin were found to be useful in this regard.

VITAMINS AND THEIR RÔLE AS COENZYMES Many enzymes require a co-factor or coenzyme for their normal function Such coenzymes frequently are relatively simple compounds and need not be protein in nature Among the most important of the coenzymes are certain of the vitamins For example, thiamine is a part of the molecule of cocarboxylase, which in the brain catalyzes pyruvic acid to acetic acid When this reaction cannot proceed, beriberi results *with its characteristic sensory nervous system manifestations* Pantothenic acid is a part of a coenzyme concerned particularly with the formation of acetylcholine, the important chemical substance concerned with the transmission of neural impulses Riboflavin is a part of a group of "yellow" enzymes which are involved in biologic oxidation reactions Finally, *para*-aminobenzoic acid is considered to be a part of an enzyme system which is necessary for bacterial growth. The bacteriostatic action of sulfonamides is exercised through the substitution *of the sulfa drug at the position in the enzyme molecule previously occupied by para*-aminobenzoic acid, rendering the enzyme ineffective *There is as yet no solid evidence* that penicillin and streptomycin act in a similar way, but it is strongly suspected that they do

A NUMBER OF METALS ARE ESSENTIAL ELEMENTS OF CERTAIN ENZYME MOLECULES Cytochrome, an important respiratory enzyme, contains iron Carboxylase contains magne-

sium and cocarboxylase contains phosphorus Both of these enzymes are concerned with carbohydrate oxidation in the brain Copper is probably an important element in an enzyme active in the formation of hemoglobin

Summarizing Comment on Rôle of Enzymes in the Physiologic Chemistry of Human Beings in Health and Disease

The foregoing brief examples of enzymic functions have been given with the purpose of emphasizing the central position occupied by enzymes in human biochemistry and physiology In investigating the neuroendocrine response to injuries of various types, some connecting link must be found between the increased amounts of the various hormones which are secreted and their final effect upon basic chemical reactions There is substantial evidence that the proximate explanation of this influence of hormones upon cellular chemical processes will be found in the intermediate enzymes which catalyze the specific but simple reactions in question Furthermore, the surgeon is certain to be carried further and more deeply into the realm of enzymology during the coming years, as the explanations for irreversible shock, burn toxemia, late intestinal obstruction, anesthesia intolerance, mechanisms of bacterial invasion, pancreatitis, and malignancy are sought.

The Use of Enzymes in Diagnosis

It would not be proper to enter into great detail here, but a few selected examples will serve as a review and prove instructive.

SERUM AMYLASE DIASTASE, AND LIPASE VALUES IN PANCREATITIS Since Elman[8] and others reported the diagnostic value of the serum amylase level in pancreatitis its use has become routine. The determination of the serum concentration of this enzyme has come to be the single most important objective criterion of the presence of the disease The urinary excretion of amylase, as well as diastase and lipase may also be increased. There are of course, other causes of elevated amylase levels (p 256)

SERUM ALKALINE PHOSPHATASE LEVEL. An evaluation of the serum alkaline phosphatase level in the presence of jaundice is, in our opinion, probably the most reliable single laboratory test in differentiating "medical" from 'surgical" jaundice In complete obstruction or virtually complete obstruction due to common duct stone, carcinoma of the pancreas or common duct stricture the alkaline phosphatase level is usually well above normal In fact if the alkaline phosphatase level is normal in the presence of jaundice, one is slow to diagnose 'surgical jaundice though it may still be present

The alkaline phosphatase level may also be increased in conditions which affect bone metabolism such as some functioning parathyroid adenomas.

SERUM ACID PHOSPHATASE LEVEL. Huggins and his associates[1-] first reported that the acid phosphatase level may be elevated in metastatic prostatic carcinoma, and this relationship has since been used as a routine aid in diagnosis (Fig 63) Fishman, Lerner, and Homburger[7] have proposed a chemical separation of the acid phosphatase of normal serum into one part originating from the prostate and another originating from nonprostatic sources, with the purpose of increasing the diagnostic sensitivity of the acid phosphatase test in patients with cancer of the prostate. However, while the serum acid phosphatase level may be normal in the presence of carcinoma of the prostate, a significant elevation in this value is virtually diagnostic of carcinoma of the prostate, usually with bone involvement.

FIBRINOLYSIN IN PROSTATIC CANCER AND OTHER CONDITIONS[22] Another enzymic derangement that has recently been emphasized in connection with carcinoma of the prostate—and with no other known malignancy—is that of the effect of prostatic fibrinolysin in a small proportion of patients with metastatic carcinoma of this organ. The substrate for prostatic fibrinolysin ap-

pears to consist of fibrinogen, fibrin, prothrombin, accelerator globulin, and probably other proteins of plasma Moreover, whereas the presence of acid phosphatase in the serum has no purpose which is apparent at this time, the presence of the prostatic fibrinolysin in blood has important consequences because this prostatic enzyme is able to digest and to destroy several of the factors required by the blood-coagulation mechanism In patients who exhibit elevated fibrinolytic levels, a pronounced decrease in the serum levels of fibrinogen, prothrombin, and accelerator globulin may lead to an hemorrhagic diathesis Interestingly enough, the level of prostatic fibrinolysin in such individuals has been shown to be influenced by the administration of estrogenic and androgenic hormones The administration of testosterone to a patient with carcinoma of the prostate can be shown to promote fibrinolysis and induce a rapid fall in the level of plasma fibrinogen, prothrombin, and accelerator globulin, and spontaneous hemorrhages may appear Conversely, the administration of estrogen produces a disappearance of fibrinolysis in the blood, and the blood-clotting factors return to a normal level

Increased fibrinolysis with diminished plasma fibrinogen has been reported in shock associated with uterine hemorrhage, and with other shock states In contrast, it will be recalled that certain patients with malignancy, particularly those with pancreatic malignancy, may exhibit an increased tendency to intravascular clotting

TRANSAMINASE LEVELS FOLLOWING INJURY During recent years there has arisen considerable interest in using measurements of the serum transaminase level as an index of tissue damage, after both myocardial infarction and various surgical operations The enzyme was first discovered by Braunstein and Kritzman,[2] in 1938, in pigeon breast muscle. In general, the magnitude of the rise following myocardial infarction appears to correlate fairly well with the magnitude of muscular necrosis The same correlation has been found following surgery, as regards the rise in the serum transaminase level and the magnitude of the operation[1] Nevertheless, the correlations referred to involve averages, in the individual patient the transaminase level is less predictable after various forms of injury

Finally, the level of this enzyme may be elevated in a wide variety of other circumstances which produce tissue necrosis, in cancer, liver disease, pancreatitis, and in lung conditions

MISCELLANEOUS OTHER ENZYME LEVELS USED IN DIAGNOSIS A diminished pancreatic enzyme content in the succus entericus constitutes evidence of pancreatic disease, and recently the measurement of the cholinesterase level in serum has been used in the diagnosis of liver disease[26]

Use of Enzymes in Treatment

The use of enzymes in surgical therapy is only in its infancy, and a number of difficulties must be solved before widespread realization of the theoretical advantages of such treatment can be realized To begin with, enzymes are protein in nature and thus are antigenic, the administration of some enzymes may result in severe anaphylactic reactions In this connection, complete purification of the enzyme preparation is desirable to remove some antigenic materials which may have no therapeutic effect A second difficulty in enzyme therapy arises from the fact that most enzymes are intracellular, and their site of action is within the cell Thus, enzymes administered parenterally would need to cross the cell membrane, and yet, the large molecular size of most enzymes makes passage through the cell membrane difficult Third, since gastric and intestinal juices can destroy many enzymes, it would presumably be necessary to administer most enzymes parenterally, rather than orally, although with an increased risk of anaphylactic shock A fourth theoretical objection is that, even were it possible to inject the enzyme parenterally and for it to cross the cell membrane, there

is grave doubt as to whether or not the enzyme would localize in that specific portion of the cell in which it might be utilized[22] For example, it is known that certain important enzymes, such as those associated with cellular respiration are found in the particulate component of the cytoplasm, in contrast to certain enzymes responsible for glycolysis, which are readily extractable in water solution Further, many of the intracellular enzymes are to be found in the mitochondria, especially those having to do with electron transport and oxygen activation A sixth consideration is that many enzymes require the co-factors or coenzymes mentioned above, it would presumably be important to be certain that when an excess of an enzyme is being administered parenterally an excess of the coenzyme is also administered.

Even so, a number of enzymes are already employed therapeutically and the use of certain of these will now be reviewed.

Hyaluronidase

This enzyme was first described as a spreading factor" present in testicular extracts, and it was later shown to be one of a group of enzymes which depolymerize hyaluronic acid and related substances. Representatives of these enzymes occur naturally in the venom of poisonous snakes and insects and as the products of various pathogenic bacteria.

Hyaluronidase causes rapid diffusion of subcutaneously injected fluids by temporarily destroying the normal interstitial barrier commonly referred to as cement substance ground substance or mesenchymal interfibrillar substance (p 104) It accomplishes this chiefly by virtue of its action upon hyaluronic acid and chondroitin sulfates, which provide the gelatinous consistency of the normal intercellular substance hyaluronic acid and the chondroitin sulfates are acid polysaccharides of giant molecular size In essence hyaluronidase depolymerizes hyaluronic acid and liquefies any barrier containing appreciable amounts of this acid[3] This reaction occurs rapidly, and the diffusion of fluid injected by hypodermoclysis is accelerated It has been observed that after a single injection of the enzyme, from 24 to 48 hr are required for complete local reconstitution of the cement substance by mesenchymal cells The processes of the natural production of hyaluronidase are not fully understood.

Commercially available hyaluronidase is in the form of a vacuum dried powdered extract of bull testis which is free from pyrogens, is destroyed by heating at 100 C for 5 minutes or by storage in alkaline media, and is stable indefinitely in a dry state at room temperature[3] Potency of the enzyme is expressed in turbidity reducing units, abbreviated to T.R U or viscosity, according to the method of the manufacturer Early commercial preparations contained impurities which occasionally produced foreign protein reactions, but with progressive purification of the enzyme such reactions have been reduced to a negligible incidence. Should inadvertent intravenous injection occur when the material is injected subcutaneously, the hyaluronidase inhibitors in the circulating blood rapidly neutralize or destroy the enzyme

In addition to its use in hypodermoclysis, the enzyme has also been used to increase the effectiveness of regional block anesthesia by making the distribution of the injected material more uniform.

HYALURONIDASE AS AID IN SURGICAL DISSECTION Streuter[21] used this enzyme as an aid in the development of planes of cleavage in different surgical procedures, particularly when accurate anatomic demonstration was difficult to obtain in the operative field because of close adherence to adjacent vital structures. He pointed out that dissection in the portal triad, lung hilum, or behind the thyroid gland may be fraught with considerable danger in the presence of fibrosis, and he stated that the injection of hyaluronidase assisted materially with the dissection The enzyme had no appreciable effect on intact pleural or peritoneal surfaces, but it

did facilitate operative procedure when it was applied directly to exposed tissues

HYALURONIDASE IN THE TREATMENT OF PARAPHIMOSIS Ratliff[18] found *injections of hyaluronidase* useful in this condition In fact, improvement occurred in 2 minutes following an injection of 150 turbidity units (dissolved in 1 ml of isotonic sodium chloride solution) at the 3 o'clock and 9 o'clock positions At the end of 12 minutes the swelling of both the edematous ring and the frenum had completely disappeared, and the prepuce was reduced with ease and without pain Four patients had been treated at the time of his report, all with good results

Streptokinase and Streptodornase (SK-SD)

Among the enzymes most valuable therapeutically are streptokinase and streptodornase, used in combination. Tillett and Garner[25] discovered that cultures of hemolytic streptococci had the capacity to promote the rapid lysis of the fibrin clot of normal human blood In later describing these early studies, Tillett[24] recalled that

"In the first experiment, 0 5 cc of a culture of a strain of hemolytic streptococcus freshly derived from a patient with acute meningitis had been added to and mixed with a few tenths of a cc of oxalated normal human plasma An amount of $CaCl_2$ sufficient to precipitate the oxalate was introduced Coagulation of the plasma developed in the normal manner However, when the tube was subsequently inspected before discarding, the contents were found to be liquid When by repetition of the experiment, mistakes in ingredients and artifacts had been excluded as accounting for the reaction, it was apparent that this strain of streptococcus possesses not only its lytic property active against red blood cells, the hemolysin, but an additional one giving rise to rapid fibrinolysis "

PREPARATION FOR USE Streptokinase and streptodornase are stable for many months in the desiccated form at temperatures of from 2 to 10° C At this temperature, solutions of a mixture of the two enzymes remain stable for seven or more days When it is desired to inject the material, from 10 to 20 ml of sterile physiologic saline solution are introduced into the vial containing the mixture of approximately 100,000 units of streptokinase and 25,000 units of streptodornase The most commonly used preparation is Varidase, produced by Lederle Laboratories, and vials containing varying amounts of the desiccated enzymes may be obtained The enzyme is used to liquefy clotted material in closed spaces (*e g*, clotted hemothorax), for the enzymatic debridement of wounds, and for other purposes that are outlined below

TREATMENT OF INTRAPLEURAL COLLECTIONS OF PUS OR BLOOD Without doubt, a most widespread use of streptokinase-streptodornase has been in the liquefaction of collections of pus or blood in the thorax, so that they could be aspirated and the lung re-expanded The injection of 100,000 units of streptokinase and 25,000 units of streptodornase in approximately 20 ml of solution will within 24 hr frequently permit the aspiration of a considerable volume of material which has been liquefied by the enzymes when no material could be aspirated previously The patient usually has a febrile reaction and is "sick" to a variable degree Although anaphylactoid reactions with near fatality have been reported,[19] the benefits gained by avoiding open thoracotomy for the purposes of removing clotted pus or blood usually outweigh the danger of a serious reaction to the enzymes

The injections may need to be repeated a number of times Frequently the enzymatic liquefaction is not adequate, and open thoracotomy must still be performed Nevertheless, with perseverance an operation can be avoided in some cases

Complications In addition to systemic reactions, a word of caution is necessary regarding the use of these enzymes in the chest to liquefy hemorrhage which has followed resection of all or part of a lung Bronchopleural fistulas have been reported to fol-

low enzymic debridement in this situation, presumably because a fibrin clot over the stump of the closed bronchus was also liquefied These enzymes do not affect healthy living tissue, but presumably permit opening of the bronchus by the means just described. Thus, one should exercise caution in using these enzymes after pneumonectomy and, to a lesser extent, lobectomy

At times it may be desirable to use SK–SD in conjunction with closed thoracotomy, the larger size of the drainage tube permitting better egress of the liquefied exudate from the chest than might be the case by aspiration with a syringe and needle

OTHER USES OF STREPTOKINASE–STREPTODORNASE The beneficial use of SK–SD in the management of contaminated or potentially contaminated wounds has been studied Immediate closure may be accompanied by a reduced incidence of infection when SK–SD is used than might otherwise be the case.

Streptokinase–streptodornase has also been used to diminish the residual exudate and clot in the perineal wound following abdominoperineal resection

Clots in the urinary bladder which cannot be successfully removed by usual methods of irrigation may be successfully liquefied by means of streptokinase–streptodornase instilled through a catheter Following injection of the enzymes the catheter is clamped for from 15 minutes to 4 hours to permit enzymatic lysis it is then opened and the bladder again irrigated When the enzymes are used immediately after prostatectomy, gentle traction on the Foley catheter may prevent them from coming into contact with actively bleeding vessels to cause further hemorrhage.

Clots occurring in drainage tubes have also been liquefied by means of instillation of these enzymes, as for example, a clot in the common duct T tube[30]

The treatment of the wound with SK–SD following excision of a pilonidal sinus was reported to be beneficial in diminishing the dead space and in the dissolution of blood clots and other debris.[15] Unquestionably a common cause of breakdown of the wound following excision of these sinuses is that the dead space is not entirely eliminated, retained blood or other exudate becomes infected through the inevitable bacterial contamination

Finally, SK–SD is used for the debridement of a variety of surface lesions which present exudate or necrotic tissue. However, this particular use of these enzymes is declining, in favor of the more recent proteolytic enzymes of the trypsin type Streptokinase and streptodornase have been used intrathecally to diminish adhesions and to reduce the incidence of hydrocephalus following various forms of meningitis, particularly tuberculous meningitis. This use has not been outstandingly effective. For prolonged effect, SK–SD may be applied in the form of a jelly in the case of surface lesions

BASIC REACTION The basic action of these enzymes is that of activating the proteolytic enzyme of plasma from its inactive state (proplasmin) into the active proteolytic enzyme, plasmin. The enzyme which accomplishes this is streptokinase The enzyme plasmin can digest fibrin and certain other proteins and transform these into soluble products

The function of streptodornase (desoxyribonuclease) is to act upon desoxyribonucleoprotein Thick purulent exudates in pleural or pericardial cavities, and in certain abscesses, consist principally of fibrin and desoxyribonucleoprotein, as well as of blood cells and other tissue degradation products The two enzymes thus act together but on different substrates to achieve liquefaction of exudates

Other Proteolytic Enzymes Used Therapeutically

In addition to streptokinase and streptodornase a number of other enzymes have been prepared which can act upon protein substances to produce lysis. Among the more important of these are trypsin and certain dialysates obtained from cultures of clostridial coliform, and pseudomonas type or-

ganisms The use of proteinase and collagenase isolated from *Clostridium histolyticum* is still in the experimental stage

Therapeutic Uses of Trypsin

One of the intriguing therapeutic enzymes is trypsin, for the favorable reports of distant effects of parenterally injected enzyme (intramuscular) have become so numerous as to render it difficult entirely to disregard the possibility of such effects.

Purified crystalline trypsin[17] is a proteolytic enzyme derived from mammalian pancreas Used topically, it digests fibrin clots and dead tissue, yielding peptides and some individual amino acids Trypsin digests the slimy and viscid coating of the desoxyribonucleoprotein of the purulent exudate and then attacks dead tissue in the lesion As the exudate thins, glucosidic assistance by means of phagocytosis is increased Bacteria in surface wounds decrease in number and, since trypsin is not bactericidal, the disappearance of bacteria would appear to be the result of a strengthening of the humoral elements of defense and a clearing of debris, which further denies a suitable culture medium to the bacteria.

TRYPSIN AEROSOL Another route of trypsin administration has been by means of aerosol for the enzymatic lysis of respiratory secretions Pulmonary secretions appear to be more viscid in the postoperative period, and this may contribute to the varying degrees of atelectasis which are often observed In an attempt to diminish the viscosity of such secretions and thus to improve drainage, Limber, Reiser, Roettig and Curtis[14] administered trypsin by aerosol to experimental animals and to a number of patients with medical pulmonary conditions of various types Twenty-three subjects were treated with aerosol trypsin, among them patients with tuberculosis, tuberculosis with bronchiectasis, bronchiectasis with complications, postoperative atelectasis, unresolved pneumonia, nonspecific pneumonitis and bronchitis, and certain other conditions Sputum volume and viscosity were usually diminished, with general improvement However, this particular use of trypsin has not had a general trial

PARENTERAL TRYPSIN. Despite the enthusiastic report by Innerfield[13] and others of beneficial results in a wide variety of conditions, including thrombophlebitis, the detailed reports of Tagnon[22] and of Taylor, Overman, and Wright[23] prompt one to maintain a skeptical attitude regarding the benefits of trypsin until further work has been done For many years it has been known that parenteral administration of trypsin in small doses results in intravascular clotting and in large doses results in a shock-like state associated with a reduction in th ability of the blood to clot, chiefly due t fibrinolysis Carefully controlled experi mental studies still would appear to suppor such observations and, indeed, most of th favorable reports have resulted from clinica studies on patients which obviously coul not be carefully controlled Innerfield an his associates[13] claim that a rapid regressio of a wide variety of inflammatory processe can be produced by the parenteral admin istration of trypsin, though even these work ers do not claim for these enzymes th prompt lysis of intravascular clots Golden' also reported favorable results

Concluding Remarks

The foregoing discussion has represented a somewhat arbitrary selection of certain examples from the prodigiously growing field of enzymology There is no question but that enzymes—whether serving by increasing our knowledge of disease, or in diagnosis, or in treatment—will assume an ever more important place in surgical practice

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Chapter 10

The Biology of Aging—A Few Notes

What is Aging?

Aging is a process—or many processes—that are in a general way correlated with the passage of time.[4] Viewed from one standpoint, it is the phenomenon of "wearing out" that we so naturally expect of most animate and inanimate objects. Yet, inanimate objects have, by and large, a life span of usefulness that is shorter than that of the more complex "living" organic systems, plant or animal. Thus, one might expect that living organic systems must possess some distinctive property which permits replacement of damaged or otherwise unserviceable component parts. This "*essential property of the living system is its ability to maintain itself, to repair and reconstitute itself. This capacity for self-synthesis sets off the living from the nonliving. If then the living organism can and does reconstitute itself continuously, how can it wear out? It is necessary to postulate that the wearing out or aging process involves a decrease in efficiency of the mechanisms for reconstitution.*"[3]

The process of aging begins at birth in some organs (*e.g.*, aorta) and at varying ages in other organs; moreover, the aging in a given organ progresses more rapidly in some persons than in others. Above all, while the manifestations of the aging process that occur in an average large group at a given age can be fairly well predicted (Fig. 72), the changes in the individual persons exhibit wide variations. And therein lies much of the challenge and the promise of intensive study of the aging process—for reasons will surely be found to explain the widely different rates of aging in different individuals.

Aging appears when growth stops and must invariably terminate in the death of the organism whether it be the bacterium, the mouse, the elephant (about 70 years), man, the giant redwood tree (3000 years) or the swamp cypress (4000 years). Even the single-cell bacterium can repair selected portions of its cytoplasm, as can the other animals and plants just listed replace or repair some parts. Yet, inevitably the vigor of the replacement or reconstitution process declines and organic dissolution ensues to complete the nitrogen cycle.

There is fragmentary evidence to support the proposition that the proximate explanation of the aging process must ultimately be found in the aging of *intracellular enzyme systems*. That is, enzyme molecules may also have a limited life span. If so, must we not inquire beyond the molecule to the atomic structure of the molecule? In this connection, it is of interest to refer to the genetic aspects of carcinogenesis, particularly as regards the genetic determination of enzyme progeny (p. 193).

The Scope of the Problem

The various facets of the problem of aging are likely to be more clearly discernible the closer one approaches them personally. Nonetheless, the physician is privileged to

see much of the extent of the problem from the time he begins his clinical training, and he gradually becomes aware that much of his practice will be concerned with the older age group of the population, with their infirmities which increase in number apace with the years

Relatively few physicians are acquainted with the large amount of related work that has been published by sociologists, psychologists, social service workers, and even political leaders [1] Though research into aging is still in its early stages, by careful utilization of information already available a longer productive and therefore happier life can be salvaged for many of the persons who have acquired the know how and wisdom of a lifetime. It has been emphasized that the "psychology of aging" is not to be misconstrued as the "psychology of the elderly" it is the relative pace or unrelieved intensity of a job that seems first to tell upon an aging man not the processes of the work itself, so long as the pace is adjusted to the reduced physiologic capacities.

The entire policy of automatic idleness at age 65 may require critical reappraisal if the total productive capacity of a nation is to be realized The job must fit the man and *vice versa* Admittedly, more care is required in the selection of both at advanced ages Yet so many individuals are now living to retirement age that the able of these must assist younger persons in the productive support of the total population

PATHOPHYSIOLOGIC CHANGES WITH AGING

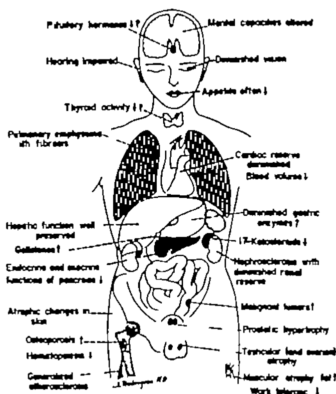


Fig 72 Most of the changes noted are often accepted as inevitable Yet the fact that any given individual may escape almost any particular one of these changes suggests that the physiologic alterations of senescence are not necessarily inevitable Therefore causes should be sought and methods of prevention developed

Some Methods of Study

A wide spectrum of investigative endeavor has been focused upon various aspects of the problem of aging. Comparative *chemical analyses* have been done Innumerable *pathologic studies* have been published with respect to both gross and microscopic findings The characteristics of single-cell organisms, simple and complex plants, lower vertebrates and different mammals have been compared. Genetic determination of life span has long interested investigators while there is some truth in the adage that to live long one must choose long lived parents, this is by no means the only or even the dominant factor The effect of *diet* has been studied, as has the effect of *climate Parabiosis* and the *lyophilization of tissues* with subsequent reimplantation have been employed *Cellular permeability* has been shown to decrease with age, possibly because of the deposition of calcium in this connection many aging tissues exhibit increased amounts of calcium. *Isotopes* have been used variously to demonstrate a decrease in physiologic activity with aging. The *functional reserve* of the different organs and capacities is reassessed again with the advent of each new technic

The Aging Process in Different Organs

A moment's reflection will remind one that certain organs or systems are far more dramatically affected by aging than are others

Chapter 11

The Liver, Gallbladder and Biliary Tract

The Liver

The liver is an exceedingly complex physiologic unit and is essential for life The seat of a surprisingly large volume of metabolic activity, its functional reserve with respect to most of its multiple rôles is so great that hepatic disease may be far advanced before clinical signs and symptoms lead the patient to seek medical advice It has repeatedly been shown that not only can a relatively large portion of the organ be excised without serious impairment of functional capacity but also that regeneration of the excised portions is rapid While it has proved tedious to work out many of the problems associated with liver function, the tremendous amount of research that has been devoted to identifying the various facets of hepatic activity has established a firm body of information in this field

Perhaps the most striking feature of "liver function" is the great variety of functions which the organ performs, rendering it impossible to measure even the several most important of these functions with a single test Thus, an ever growing "battery" of tests is employed in evaluating the status of liver function

Functional Anatomy of the Liver

The gross functions of the liver are shown in Figure 73 and the schematic presentation of a liver lobule is shown in Figure 74 Note that the hepatic artery and the portal vein both approach the lobule at its periphery, from whence also flows the bile, these three structures—hepatic artery, portal vein, and bile duct—are referred to as the *portal triad* In contrast, the central vein collects the blood and carries it to the hepatic vein As will be seen later, portal venous hypertension may occur from obstruction to blood flow through the hepatic vein (suprahepatic) or from obstruction within the liver (intrahepatic, usually from cirrhosis), or from infrahepatic causes such as portal vein thrombosis (Fig 75)

Each lobule, then, contains elements of the three primary systems of the liver the *vascular system*, the *parenchyma*, and the *bile collecting system* Vascular disorders associated with hepatic blood flow have to do chiefly with the blockage of total venous flow, and will be considered further in connection with cirrhosis Parenchymatous disorders, resulting from involvement of the liver cells themselves, may result from anoxia, viral infection, nutritional deficiencies, and other causes Bile duct system disorders frequently require surgical intervention, in fact, they constitute the largest of the three groups, as far as surgical management is concerned

Liver Functions

Various of the physiologic activities of this organ have been touched upon in previous pages, but certain of the more prominent ones may be listed

1 METABOLISM OF FOODSTUFFS

a Carbohydrate Through the formation of glycogen the liver provides a readily mobilizable fuel Hypoglycemia is a major feature of hepatic insufficiency

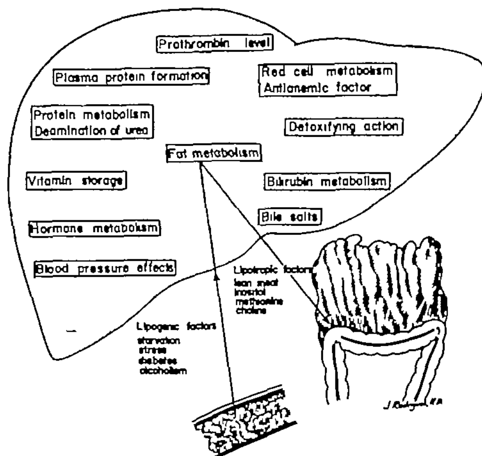


Fig 73 The liver is the center of a major segment of the metabolic activity of the body It has a tremendous functional reserve and a striking capacity to regenerate Yet, when hepatic function is reduced below a critical level, death ensues at times due to hypoglycemia

b *Protein* The liver forms urea by deaminizing amino acids Following hepatectomy the blood urea nitrogen (BUN) falls and the amino acid concentration rises

c. Fats The rôle of the liver in fat metabolism is less clear cut. However fat mobilized from the depots in adipose tissue passes to the liver, where the neutral fat is processed for use *Lipogenic factors* (*e g* , starvation, diabetes) increase the movement from fat depots to the liver *Lipotropic factors* (*e g* choline methionine protein) promote transport of fat from the liver to depots (Fig 73)

2 STORAGE The liver stores certain materials such as glycogen and vitamin A.

3 SYNTHESIS The liver is the principal or only source of certain important substances as for example plasma proteins (albumin globulin fibrinogen) and prothrombin the latter is essential for normal blood coagulation

4. DETOXIFYING ACTIVITIES The liver acts upon a variety of compounds to assist the body in minimizing toxic effects This activity consists in three types of chemical activity First, the liver may actually metabolize (oxidize) or destroy certain drugs such as strychnine and sodium pentobarbital Second, the liver may combine the toxic or "active" (in the case of free hydrocortisone) substance with a second substance the resulting "conjugate" being no longer active metabolically Third the conjugation process may not render the "toxic" compound less toxic to the body but it may render it more rapidly excreted in the urine perhaps by increasing its water solubility The liver is particularly important in the metabolism of various hormones.

5 BILE FORMATION (FIG 76) Following

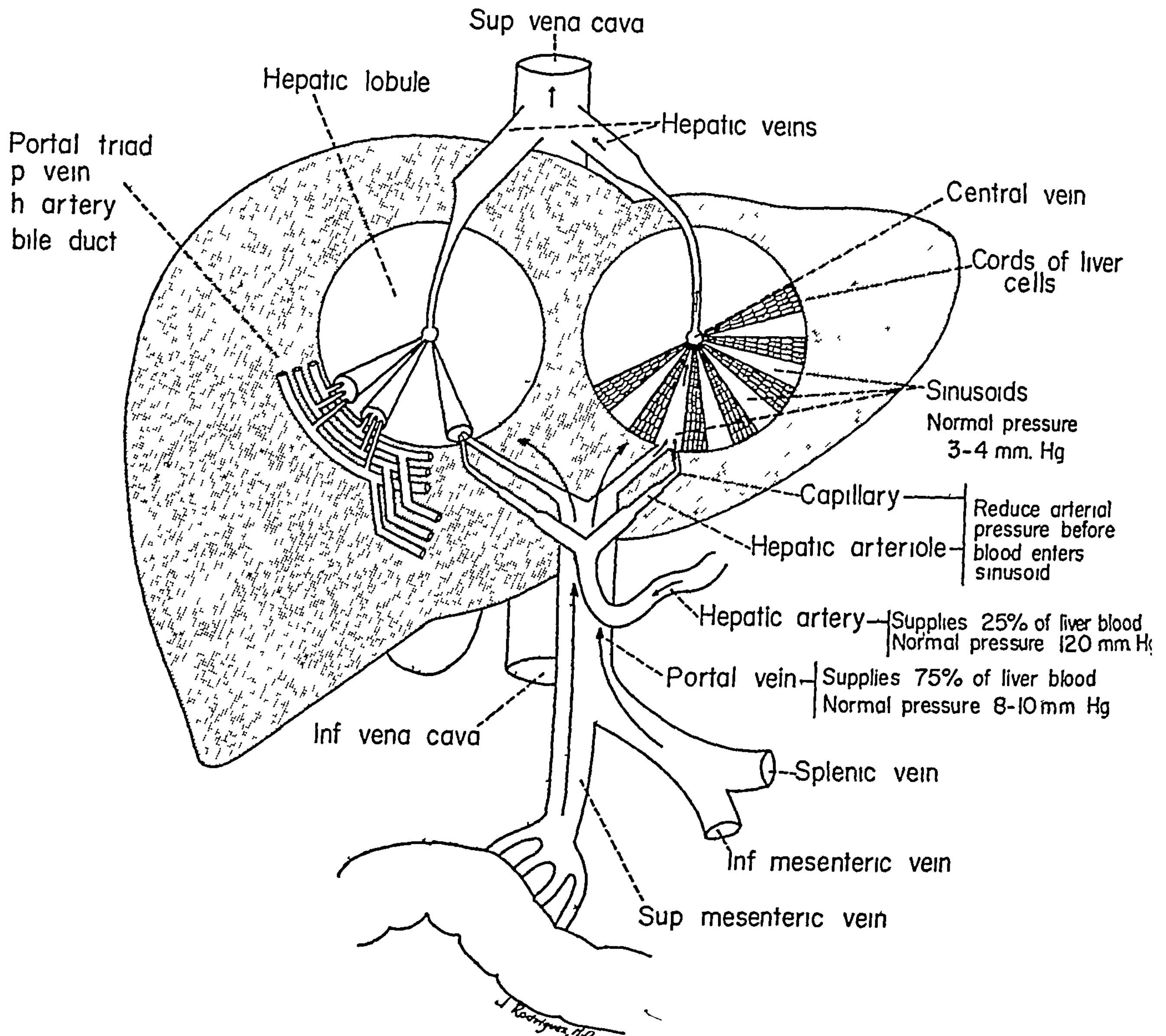


Fig 74 The contributions of the several tributaries to the hepatic blood flow are indicated Hepatic circulation and, consequently, hepatic function are influenced by many diseases

hepatectomy the animal becomes jaundiced within a matter of hours Whereas bilirubin can be formed outside the liver, only this organ is normally concerned with its excretion Bile is alkaline in reaction and may range in daily volume from 500 cc to 1500 cc (average about 800 cc), as may be ascertained by T-tube drainage when the distal common duct is occluded The more important constituents of bile are *bile pigments* (derived from bilirubin), *bile salts* (important in fat digestion), and *cholesterol* The bile pigments are derived from the breakdown of red cells elsewhere in the body and brought to the liver for excretion The bile acids and their bile salts are not excreted from the body but are passed with the bile into the intestinal tract, from which they are reabsorbed into the blood stream and returned to the liver The bile salts are considered to be important in maintaining cholesterol in solution, cholesterol being precipitated when the normal ratio of bile salts to cholesterol in bile is reduced Bile salts enhance the activity of pancreatic digestive enzymes, promote the absorption of fat products and vitamin K, and act as a secretagogue to increase bile formation When bile salts fail to enter the bowel, a significant part of ingested fat is not ab-

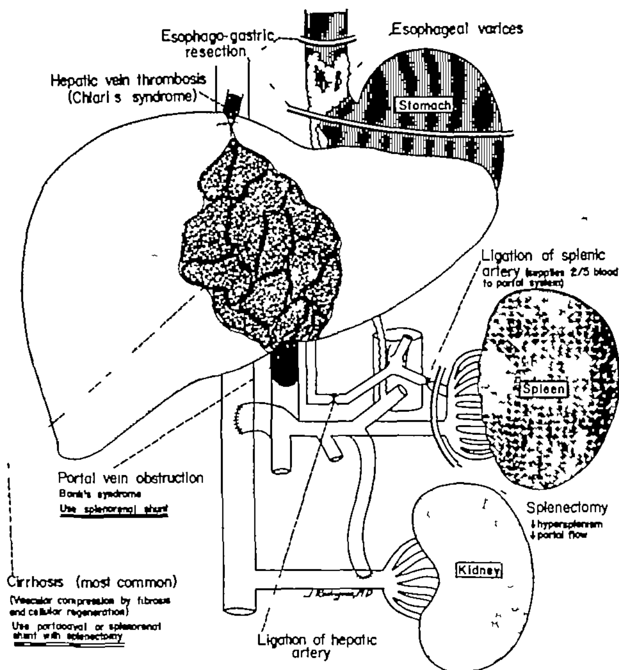


Fig 76 The variety of operations proposed for the management of bleeding esophageal varices in portal hypertension attests the unpredictability of a given operation in a given patient.

sorbed and is lost in the feces. So far as is known bile salts are produced, concentrated, and destroyed only in the liver Cholesterol is normally present in blood and bile Its endogenous source has not been definitely defined nor has its rôle in general metabolism It is believed by many that the cholesterol ring is a precursor of steroids, but Lipmann[16] has pointed out that in synthesizing even complicated compounds the body usually prefers to employ relatively simple structural units

The functions of the bile, with its bile salts, are described elsewhere in this volume.

6 MISCELLANEOUS OTHER ACTIVITIES Hepatic function is important also for the

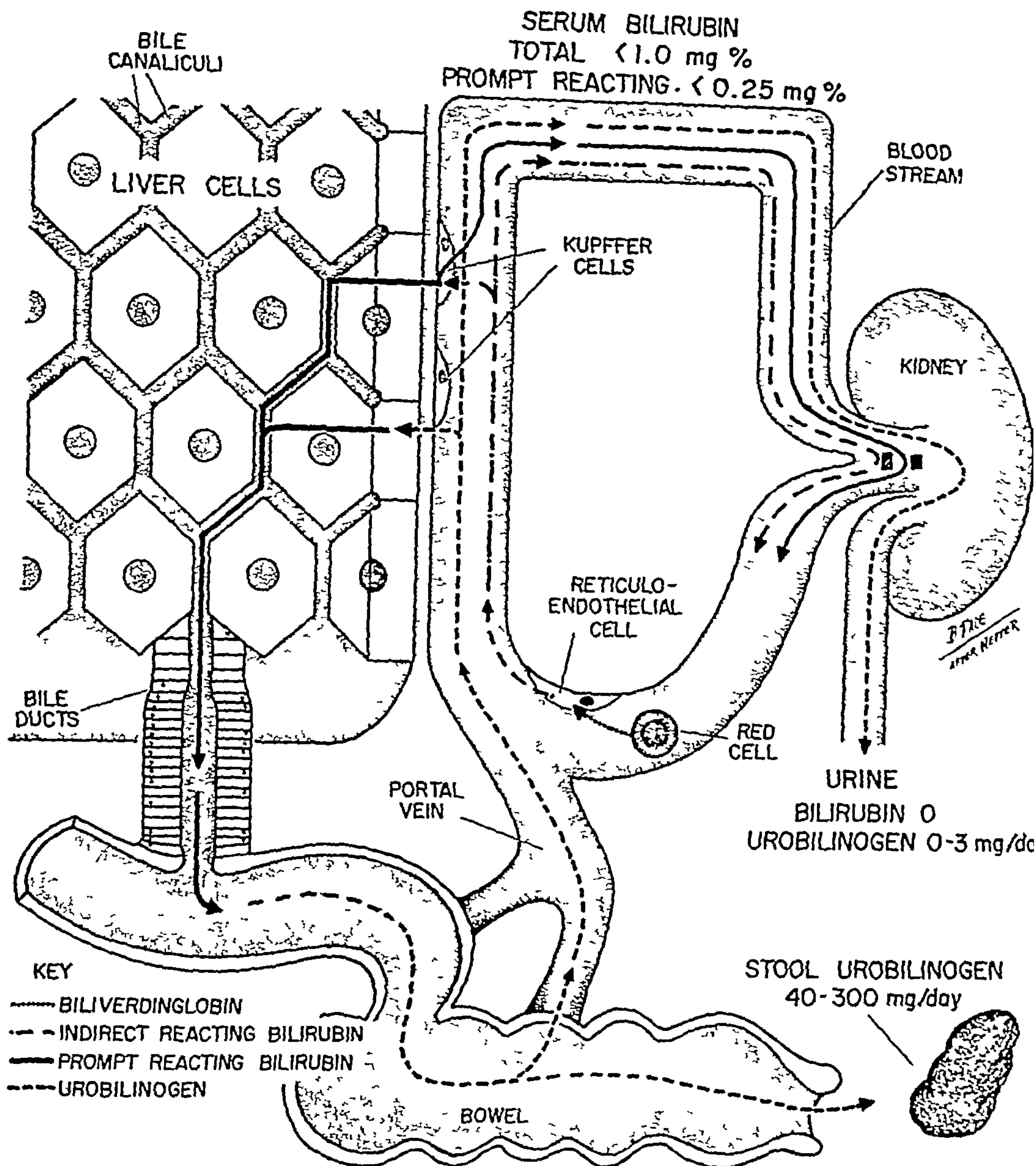


Fig 76 Normal circulation of bile pigment Urobilinogen is present, and the stoo pigmented (Modified from NETTER, F H *The Ciba Collection of Medical Illustratu* Part III, Vol 3, Summit, N J Ciba Pharmaceutical Products, Inc, 1957)

maintenance of a normal blood pressure, antibody function, red cell metabolism, and numerous other metabolic purposes (Fig 73).

Liver Function Tests

The following measurements reflect the efficiency of several different liver activities

HISTORY AND PHYSICAL EXAMINATION Of course, the clinical evaluation of the patient does not constitute a "function test" in the narrow sense of the term, but in practice it is frequently the most useful test available, especially where tests are being relied upon to distinguish "medical" from "surgical" jaundice

SERUM PROTEIN LEVEL AND ALBUMIN LIN (A G) RATIO Since the liver syr these proteins, the total serum prote is frequently depressed in liver dise the A G ratio reversed This reversa to the fact that whereas the album declines, the globulin concentration preserved or even elevated The serum albumin concentration is a mately 4 to 5 gm per 100 cc and globulin 2 5 to 3 5 gm, with a total protein level of from 7 to 8 5 gm

SERUM BILIRUBIN LEVEL Total seru rubin is determined by treating the with diazo reagent in the presence o ficient alcohol to catalyze the reaction

not precipitating protein Direct bilirubin is determined by the same method but alcohol is omitted. Readings are made exactly 1 minute after addition of the reagents, direct bilirubin so measured being termed the "one minute" direct reading.

Normal values for total bilirubin are 0 1 to 1 3 mg per 100 cc of serum The direct bilirubin level should usually be less than 0.25 mg. per 100 cc, and the direct bilirubin level is a somewhat more sensitive indicator of liver disease than is the total bilirubin level An elevated total bilirubin level may of course reflect increased red cell destruction, as well as disease of the hepatobiliary tract

When the serum bilirubin level exceeds 2 0 mg per 100 cc, the jaundice of the sclerae may usually be detected when the patient is viewed in natural light. The lesser grades of jaundice are notoriously difficult to discern in artificial light

3 The *conjugation of bilirubin to a glucuronide* by liver cells is being found to represent an important aspect of the metabolism of this pigment. Bilirubin appears to be transported (on albumin?) to the liver, where it is rendered more water soluble by the conjugation process. Thus, in obstructive jaundice the chief pigment in the plasma is a water soluble bilirubin conjugate which gives the "direct" van den Bergh reaction These relationships have recently been re-examined (Billing, B H, and Lathe, G H Bilirubin metabolism in jaundice Am J Med, **24**: 111, 1958)

4 SERUM CHOLESTEROL CONTENT Obstruction of the common duct may be associated with a high total cholesterol, but with a normal ratio of esterified to total cholesterol. Hepatitis may be associated with a normal or low total cholesterol, with a decreased ratio of esterified to total cholesterol. However the ratio may fall considerably in obstructive jaundice also

5 BROMSULPHALEIN TEST For this test 5 mg. per kg. of body weight of this substance is injected intravenously, and blood is collected at 30 or 45 minutes from the opposite arm. The serum is treated with alkali, which brings out the color of the dye, and the color density is measured in a comparator or photocolorimeter More than 10 per cent retention at 30 minutes or more than 5 per cent at 45 minutes is considered abnormal This is among the more sensitive and reliable tests of liver function, and it is particularly helpful in the absence of hyperbilirubinemia

6 UROBILINOGEN IN URINE. In the biliary tract bilirubin in oxidized to biliverdin and, in the bowel, bilirubin is reduced to urobilinogen Normally the pigment is partially reabsorbed from the bowel and again excreted in the bile only a small amount appearing in the urine, however, in hemolytic jaundice the large amounts of urobilinogen formed in the bowel from the flow of excessive bile pigment may so increase the amount of urobilinogen reabsorbed into the blood that the liver cannot re-excrete rapidly enough to prevent an increased excretion in the urine In contrast, if jaundice is associated with an absence of urobilinogen in the urine, obstruction of the biliary tract must be considered likely—since bilirubin cannot reach the bowel to yield urobilinogen (Figs 77 to 79)

7 SERUM PROTHROMBIN LEVEL. Since the liver synthesizes prothrombin from vitamin K, the prothrombin level is often diminished in liver disease, as reflected in a reduced coagulability of the blood. The prothrombin values are expressed on the basis of the time required for clotting or on the basis of the percentage of the normal (control) prothrombin level. The standard must be checked and maintained by each hospital

If the prothrombin level is found to be low but responds promptly to the administration of vitamin K liver functional reserve is probably fairly good if response to this therapy is slight or absent, serious liver disease must be suspected Accordingly, a low prothrombin level associated with purely extrahepatic biliary obstruction frequently rises promptly after a few days of vitamin K therapy, for common duct obstruction

does not produce severe liver damage until after weeks or months have elapsed In contrast, severe liver damage associated with viral hepatitis or cirrhosis may preclude adequate response of the prothrombin level to treatment Massive carcinomatosis of the liver may also be associated with a refractory low prothrombin level (and increased bromsulphalein retention), at times with essentially normal flocculation studies

8 FLOCCULATION TESTS (CEPHALIN AND THYMOL) These tests are empiric and are used to distinguish jaundice due to liver cell damage, as in hepatitis, from jaundice due to obstruction (of the larger bile ducts), which does not immediately cause cellular damage The tests depend upon an increase in globulin (and, in particular, gamma globulin) and a fall in serum albumin If these tests are strongly positive soon after jaundice appears, hepatitis is suggested, if the tests are negative initially but thereafter gradually become positive after several weeks of jaundice, mechanical biliary obstruction, perhaps by common duct stone or carcinoma of the pancreas, is suggested—for gradually the back pressure dilates the bile ducts and may eventually produce extensive pressure necrosis or atrophy of the parenchyma Even so, the tests are usually far more positive in hepatitis than in obstructive jaundice of even long duration

Unfortunately, all too often the flocculation (and turbidity) tests are neither strongly positive nor definitely negative and, while the intermediate degrees may suggest some liver damage, they may not materially assist in differentiating medical jaundice from surgical jaundice

9 SERUM ALKALINE PHOSPHATASE LEVEL. The normal serum alkaline phosphatase level is from 1 to 4 Bodansky units in adults and from 5 to 14 units in children This is often the single most helpful *laboratory* test, (history and physical examination are superior to any tests) in differentiating hepatitis from obstructive jaundice If the serum phosphatase level is elevated, we consider obstructive jaundice more likely than hepatitis, or, to state this differently, we have misgivings about operating upon a jaundiced patient if the alkaline phosphatase level is normal, lest the patient prove to have hepatitis and do poorly postoperatively Still, this test is not infallible

The serum alkaline phosphatase level may also be elevated in conditions other than liver disease (*e g*, hyperparathyroidism)

10 SERUM MUCOPROTEIN LEVEL This test was proposed by Greenspan and Dreiling[12] as a measure for differentiating hepatogenic from obstructive jaundice The term *serum mucoprotein* designates a carbohydrate-rich protein fraction which comprises approximately 1 per cent of the total serum proteins in the normal state The average serum mucoprotein concentration is from 48 to 75 mg per 100 cc in normal men and from 40 to 70 mg per 100 cc in women A reduction in the serum mucoprotein level was observed in approximately 80 per cent of 180 patients with infectious hepatitis, homologous serum hepatitis, or portal cirrhosis, but in only 2 per cent of 125 patients with various forms of obstructive biliary tract disease Approximately 90 per cent of 100 patients with metastatic hepatomegaly had an increased mucoprotein level

The mucoprotein level was not interpreted as a specific or reliable index of liver function, but the diagnostic value of a single determination compared favorably with that of the A/G ratio, cephalin flocculation, thymol turbidity, alkaline phosphatase, and prothrombin time

Comment on liver function studies As one might conclude from the number of tests used to measure hepatic function, no one test measures all functions. In fact, all available tests often are inadequate to permit an accurate diagnosis preoperatively Again, the liver damage must often be marked before functional impairment is demonstrable, so great is the physiologic reserve of this organ Yet, this is not to imply that liver function studies are not helpful, for they are

Acute Liver Failure ("Hepatic Insufficiency")

Complete failure of hepatic function is seen in the experimental animal following complete extirpation of the liver, and it is occasionally met clinically as acute hepatic failure or hepatic decompensation following prolonged disease When the liver is removed in animals there is a progressive fall in the blood sugar level and the hypoglycemia may reach 40 mg. per 100 cc or less In the dog there is muscular weakness, followed by convulsions, coma and death Jaundice occurs if the animal lives for 6 hours or more The administration of glucose intravenously may render a dog alert where a few minutes previously he was in coma.[26] Immediately following the injection the blood sugar reaches a high level but it then decreases rapidly and the symptoms of hypoglycemia reappear Thus, the liver is the central organ for maintaining a normal level of blood sugar There is seen a progressive fall in the blood urea because of the fact that the liver is the chief site of deamination of amino acids, and it is apparently the only organ in which urea is formed. As the hours pass following experimental hepatectomy, the coagulability of the blood is depressed, owing mainly to a marked decrease in the concentration of plasma prothrombin and perhaps also to a decrease in plasma fibrinogen Finally—even if the blood sugar is kept normal by the continuous infusion of glucose—restlessness, dyspnea and vomiting occur the animal becomes ataxic and anuria is followed by death often quite suddenly

In patients the initial symptoms of acute hepatic failure are somewhat indefinite The individual feels ill and complains of anorexia and nausea. A drowsy state and apathy are associated with extreme weakness Vomiting may be persistent and jaundice becomes severe The serum bilirubin level may rise to from 20 to 30 mg. per 100 cc. The blood prothrombin level falls markedly and bleeding may occur into the skin and mucous surfaces The blood urea level is at times low (less than 8 mg per 100 cc) The pulse rate, temperature and respiration are unaffected until late in the disease, when the pulse accelerates and the temperature rises Late in the disease the blood pressure frequently falls and, though the patient may often appear to be quite alert, a persistently lowered blood pressure with a systolic level in the neighborhood of 70 mm Hg is often a sign of irreversible liver failure Anuria commonly occurs and in some cases the so called hepatorenal syndrome is frankly present, there is a diminished volume of urine, a retention of nitrogenous substances in the blood, and finally even complete anuria. In our limited experience, the treatment of renal failure associated with hepatic insufficiency by means of the artificial kidney has achieved little.

Obviously liver failure presents biochemical and clinical phenomena of great diversity, for not only are the functions of the liver deranged but those of other organs are also profoundly affected by the hepatic disease. Accordingly, the usual manifestations of severe liver disease—such as ascites, hemorrhage and jaundice—may be accompanied by violent symptoms of extrahepatic origin, among these are convulsions and delirium often terminating in coma. Pulmonary congestion or circulatory collapse may reflect cardiac or peripheral vascular failure and the body temperature may reach 106 F

THE PRECIPITATION OF HEPATIC COMA. Acute hepatic decompensation will be considered again in connection with the management of cirrhosis, but it may be remarked here that the ingestion of large amounts of animal protein (meat intoxication) may precipitate hepatic coma in cirrhotic or other individuals who have borderline hepatic compensation (Table 12) It has been found that the cerebral manifestations are due to a defect in the brain metabolism of the increased amounts of ammonium ion entering the circulation.

TABLE 12 Some Facts about Ammonia Intoxication in Man

I Ammonia is normally present in the following concentrations (per 100 cc) (a) Peripheral vein, 50 gamma, (b) Portal vein blood, 250 gamma, (c) Hepatic vein blood, 80 gamma, (d) Renal vein blood, 100 gamma
The liver removes ammonia from the blood, and the kidney contributes ammonia to the blood The major sources of ammonia are deamination in protein metabolism, formation from glutamine in the kidney, and absorption into the portal system of ammonia formed by gastrointestinal urease activity The synthesis of urea in the liver is the final pathway for excretion of ammonia, and thus the liver protects against the high ammonia levels found in the portal vein

II Disordered consciousness and coma, accompanied by electroencephalogram (EEG) changes, result from excessively elevated peripheral blood ammonia levels

III Hepatic insufficiency predisposes to ammonia intoxication because the protective urea formation is impaired Meat ingestion, gastrointestinal bleeding, or ammonium chloride administration may produce severe neurologic manifestations and even coma Oral antibiotics may reduce the intestinal flora and diminish the ammonia formation in the intestine, a matter of importance in patients with borderline hepatic function This is especially pertinent following portacaval shunt where not only may liver reserve be impaired but also the "filtering" effect of the liver lost as the portal blood enters the vena cava and passes to the brain (From McDermott, W V Jr, Adams, R D, Riddle, A G Ammonia metabolism in man Ann Surg, **140:** *539*, 1954)

Some Pathologic Changes in Hepatic Disease: Further Discussion

PARENCHYMATOUS DISORDERS HEPATITIS AND CIRRHOSIS Injury to the liver parenchyma is usually caused by infectious agents, anoxia, toxic chemicals, metabolic disorders, and nutritional deficiencies Furthermore, more than one etiologic agent may be active in the same disease process For example, a liver depleted of protein but increased in fat, due to an inadequate dietary intake, may be particularly susceptible to damage by toxic or other agents

It is not easy to distinguish which agent caused the cellular changes observed at microscopic examination of the diseased liver and, incidentally, there may be a marked disparity between what is found at liver punch biopsy during life and what is found at postmortem examination There is always the possibility, moreover, that microscopic changes ascribed to various aspects of liver disease may represent only artifacts

Ingelfinger[15] noted that one of the most important factors that determines the amount of damage sustained by the liver in any particular assault is the degree of acuteness of the disorder rather than the nature of the disorder When there has been injury to the hepatic parenchyma one finds cellular damage, edema, leukocytic infiltration, and hemorrhagic phenomena of variable intensity If an attack is particularly severe, the liver cells cannot survive and they undergo complete destruction In fact, in the more fulminant forms of viral hepatitis the stroma may be swept clear of parenchymal cells, which are replaced by hemorrhages in the center of each lobule and by densely packed inflammatory cells at the periphery The liver may be relatively normal in gross size, but the consistency is flabby and the cut surface represents a "nutmeg" appearance In a less acute process, parenchymatous destruction may be incomplete and the patient may not die immediately, in fact, he usually survives If the patient does survive, however, excessive fibrotic changes may occur and present a hard, small and irregular or knotty liver

There remains some question as to whether diffuse parenchymatous hepatitis progresses to a portal cirrhosis, but certain evidence indicates that it may do so However, the average case of portal cirrhosis does not follow acute hepatitis or any other obvious hepatitis Instead, the onset of the disease is insidious and progresses slowly Very commonly there is a history of an in-

adequate dietary intake, often associated with, and perhaps the result of, chronic alcoholism. At an early stage there is fatty infiltration which produces a large liver of relatively normal shape and consistency Later on there is some loss of hepatic cells, and fibrosis develops throughout the liver in massive strands. Attempts at repair are disorderly Cellular infiltration, pigment deposits, and bile duct perforation are common The essential feature of the whole process is complete derangement of the normal hepatic architecture The neat lobules with their symmetrically placed central veins give way to interlacing bands of connective tissue containing irregular strands of parenchyma with a haphazard blood supply Eventually the fatty infiltration and fibrosis combine to produce, if sufficiently prolonged, a large, hard and diffusely nodular liver The liver may thereafter remain large, or it may shrink in size as the dense connective tissue contracts, resulting in a small, hard atrophic form of portal cirrhosis

The relationship of the dietary intake to hepatic structural changes was discussed briefly in the section on nutrition Under various conditions in which fat is mobilized and deposited in the liver the lipid content of the liver increases hepatic function may be altered, and fibrotic changes may ensue Again the degree of fat deposition in the liver can be diminished—or fat more rapidly mobilized from the liver—by the administration of dietary lipotropic agents such as choline methionine, and inositol A deficiency of such lipotropic factors in the diet of experimental animals results in a diffuse fibrosis which in some important respects resembles portal cirrhosis in man. This usually follows an initial fatty infiltration of the liver For this reason it is reasonable to accept fatty infiltration as an important feature of dietary cirrhosis in both man and the laboratory animal though the relationships among cellular damage fatty infiltration and fibrosis must await further study

Biliary Ductal Disorders: Obstruction (Fig 83)

PARENCHYMAL CHANGES IN BILIARY OBSTRUCTION Obstruction to the biliary outflow, as might be caused by a common duct stone, stricture of the common bile duct, or carcinoma of the head of the pancreas is followed gradually by various degrees of atrophy of the liver Furthermore, the changes which take place will depend upon whether or not ascending infection is present. Normally, the pressure in the common bile duct and biliary tree ranges from a low of approximately 10 cm. H_2O when the sphincter of Oddi is relaxed by cholecystokinin following a meal to approximately 20 cm. H_2O as the gallbladder fills with bile during fasting In complete biliary obstruction this pressure rises to approximately 30 cm H_2O, following which the secretory pressure of the liver cells is exceeded and bile output diminishes and finally ceases However, if the normally distensible gallbladder is present to remove water and thus to concentrate the bile, the rise in pressure is less acute

In common bile duct obstruction the parenchymal cells lining the bile capillaries are subjected to pressure from the distended bile channels This pressure concomitantly diminishes cellular oxygenation and nutrition, due to the fact that the inflow from the portal vein is also somewhat diminished by the pressure exerted by the bile in the biliary tree If obstruction is prolonged, the parenchymal cells undergo varying degrees of atrophy, this may be observed when the obstructed common duct is opened at operation, for the escape of a large volume of "white bile" may result in a visible reduction in liver size This extensive replacement of parenchyma by diffuse ductal enlargement may be demonstrated at autopsy by filling the biliary tree with a radiopaque medium and making roentgenograms Under these circumstances the liver will usually be enlarged and firm but not hard Atrophy of

the liver parenchyma in the presence of long-standing complete or almost complete biliary obstruction is similar to the atrophy of the cerebrum which occurs in the presence of internal hydrocephalus

While parenchymal damage can result from simple pressure without infection, cholestasis is frequently associated with cholangitis, often manifested by chills and fever In our experience, such infection is more frequently a result of incomplete obstruction caused by a common duct stricture or stone rather than of complete obstruction due to tumor The cholangitis affects not only the common bile duct, but it frequently extends into the finer biliary channels of the liver itself, producing intrahepatic suppuration This may result in further bile blockage by inspissated material in the bile canaliculi, even after the common duct obstruction has been relieved It has been pointed out that such inspissated bile may result in late jaundice following an attack of hepatitis, and may give the impression of a relapse when in fact it amounts to a purely mechanical or obstructive jaundice Adrenocorticotropic hormone (ACTH) and hydrocortisone have been used to clear these plugs

Unless infection is overwhelming, chronic obstruction of the common bile duct results in biliary cirrhosis The liver is likely to be large and firm, since parenchymal destruction is limited, and new bile ducts, cellular infiltration, and fibrosis contribute to the hepatic mass In contradistinction to portal cirrhosis, the parenchymal cells are not primarily affected in biliary cirrhosis Thus, the structure of the liver, though distorted, is not completely destroyed, and the intrahepatic circulation preserves some of its original configuration Eventually, however, the sinusoidal circulation may be sufficiently impaired to expose the parenchymal cells to undernutrition and anoxia Under these conditions the structural abnormalities of portal cirrhosis may gradually be superimposed upon those of biliary cirrhosis

Differential Diagnosis of Jaundice (Figs. 77 to 79)

From the clinical standpoint, the most important consideration is that of differentiating obstructive jaundice, which may be successfully managed by surgical intervention, from nonobstructive or hepatocellular jaundice, in which surgery is contraindicated and at times may even be fatal For this reason, the problem is frequently spoken of as that of differentiating "surgical" from "medical" jaundice This is not to state that it is not also important, for prognostic purposes, to proceed further and to identify the precise cause of either medical or surgical jaundice Nevertheless, in planning management, the decision as to whether or not laparotomy is indicated is often the crucial one

THE HISTORY AND PHYSICAL EXAMINATION There can be no question that the most important aid in distinguishing medical from surgical jaundice is the clinical evaluation of the total patient The history is frequently more helpful than is the physical examination Laboratory data are apt to be only "compatible with" or confirmatory of the diagnosis reached on the basis of clinical data

Medical jaundice is most frequently the result of infectious hepatitis, homologous serum jaundice, hemolytic anemia, or cirrhosis Nevertheless, certain drugs (*e.g.*, chlorpromazine), and conditions such as hypoxia, leptospiral infection, schistosomiasis, or other conditions may account for the occasional case In medical jaundice there is usually some bile in the stools, though this is not always true, particularly during a portion of the natural course of infectious hepatitis Inquiry should be made regarding transfusions, needle punctures, or exposure to known cases of hepatitis The stigmata of cirrhosis are also sought for (Fig 80)

One frequently makes the diagnosis of medical jaundice chiefly by excluding possible causes of surgical jaundice In other words, if one cannot find a definite indication for surgery, then the diagnosis becomes,

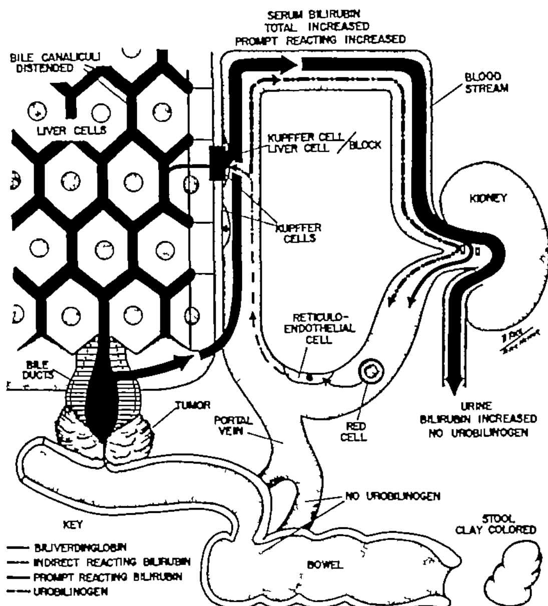


Fig 77 Urobilinogen is absent and the stool is acholic (Modified from NETTER, F H *The Ciba Collection of Medical Illustrations* Part III Vol. 3 Summit, New Jersey Ciba Pharmaceutical Products Inc 1957)

by exclusion medical jaundice at least for the moment.

By and large the cases of *surgical jaundice* will be due to a common duct *stone* to an intrinsic or extrinsic *tumor* involving the extrahepatic biliary tree, to postoperative or other *stricture* of the common duct or, occasionally to *fibrosis* in the region of the sphincter of Oddi perhaps secondary to pancreatitis (Fig. 92) The common duct stone will frequently be accompanied by a history of previous attacks of cholecystitis, though this is not always true and the silent common duct stone causing jaundice is well known. The probability of common duct stone is increased if the jaundice is intermittent if it is associated with chills and fever and if the gallbladder is not much enlarged If there was a previous operation (usually cholecystectomy), the history of profuse bile drainage from the wound beginning shortly after operation, followed by

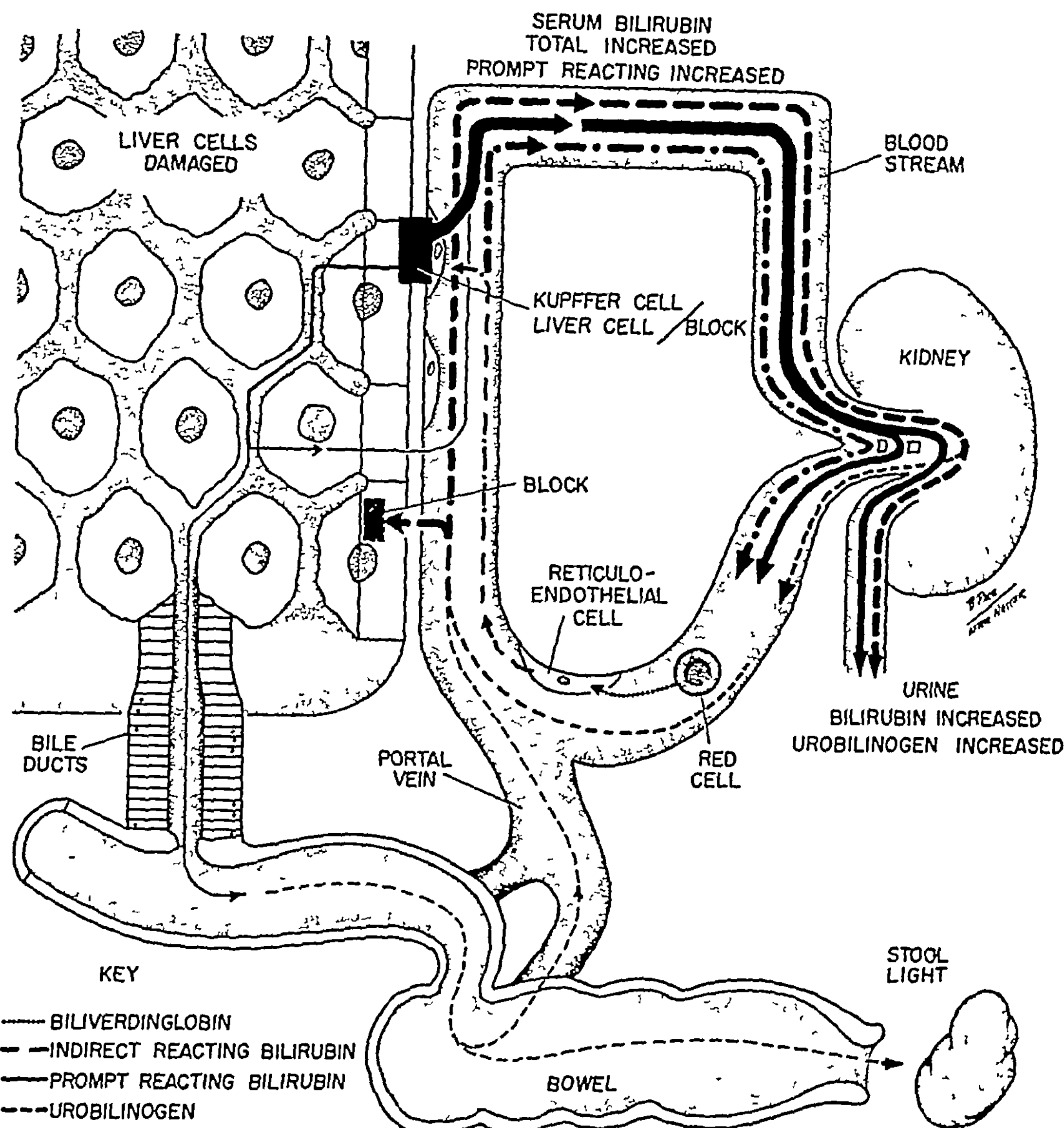


Fig 78 Urobilinogen formation decreased but urine content often increased Stool pigmentation decreased (Modified from NETTER, F H, *The Ciba Collection of Medical Illustrations*, Part III, Vol 3, Summit, New Jersey Ciba Pharmaceutical Products, Inc, 1957)

an increasing jaundice as bile flow diminished, constitutes evidence of common duct injury with resulting stricture Of course, the color of the stools is dependent upon the amount of bile flowing into the bowel, if the external fistula is complete, neither will the patient be jaundiced nor will there be bile in the stool It is only when the common duct becomes strictured by fibrosis and the defect in it closed that bile is no longer lost through the wound or stool, and the patient becomes jaundiced (It was seen in Chapter 2 that the continued loss of the entire bile flow through a biliary fistula may seriously deplete the patient of extracellular electrolytes unless precautions are taken) Carcinoma of the head of the pancreas may be suggested by the insidious development of jaundice in an elderly subject, though some cases are associated with pain and some patients are relatively young Since stones often have not been present to cause scarring with attendant inability of the diseased gallbladder to distend, this organ may exhibit marked, rela-

Circulation of Bile Pigment in Hemolytic Jaundice

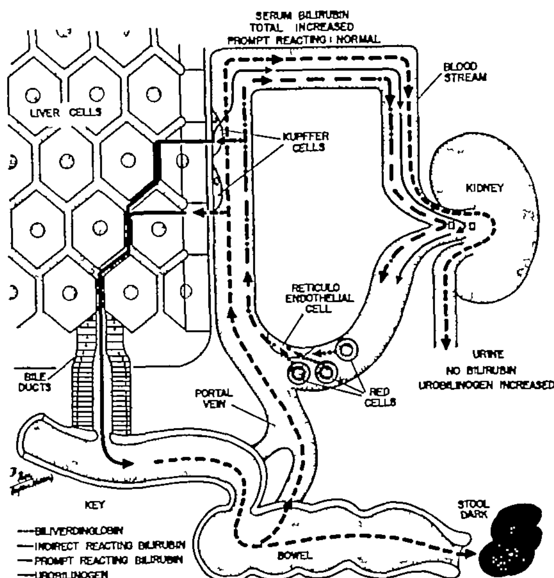


Fig 79 In hemolytic jaundice there is no bile in the urine the stools contain abundant pigmentation and the alkaline phosphatase level is usually not elevated. (Modified from NETTER, F H., *The Ciba Collection of Medical Illustrations* Part III Vol. 3 Summit, New Jersey Ciba Pharmaceutical Products, Inc 1957)

...ely painless enlargement (Courvoisier's ...)

LABORATORY DATA. After all possible information has been gleaned from clinically ...ulable findings and a tentative impression of the probable diagnosis arrived at, laboratory data may be of much assistance—for whereas neither the clinical evaluation nor the laboratory reports may be conclusive separately together they may complement each other to provide an accurate profile of the changes produced by the disease process and yield valid diagnostic conclusions.

THE DIAGNOSTIC VALUE OF PROLONGED OBSERVATION OF THE JAUNDICED PATIENT IN DOUBTFUL CASES Jaundice rarely constitutes an emergency, and if the diagnosis is in doubt it is usually wise to complete a careful initial evaluation of the case, including liver function studies, and then to observe the patient over a period of days A few days delay in operation upon the patient who has surgical jaundice entails little risk for it

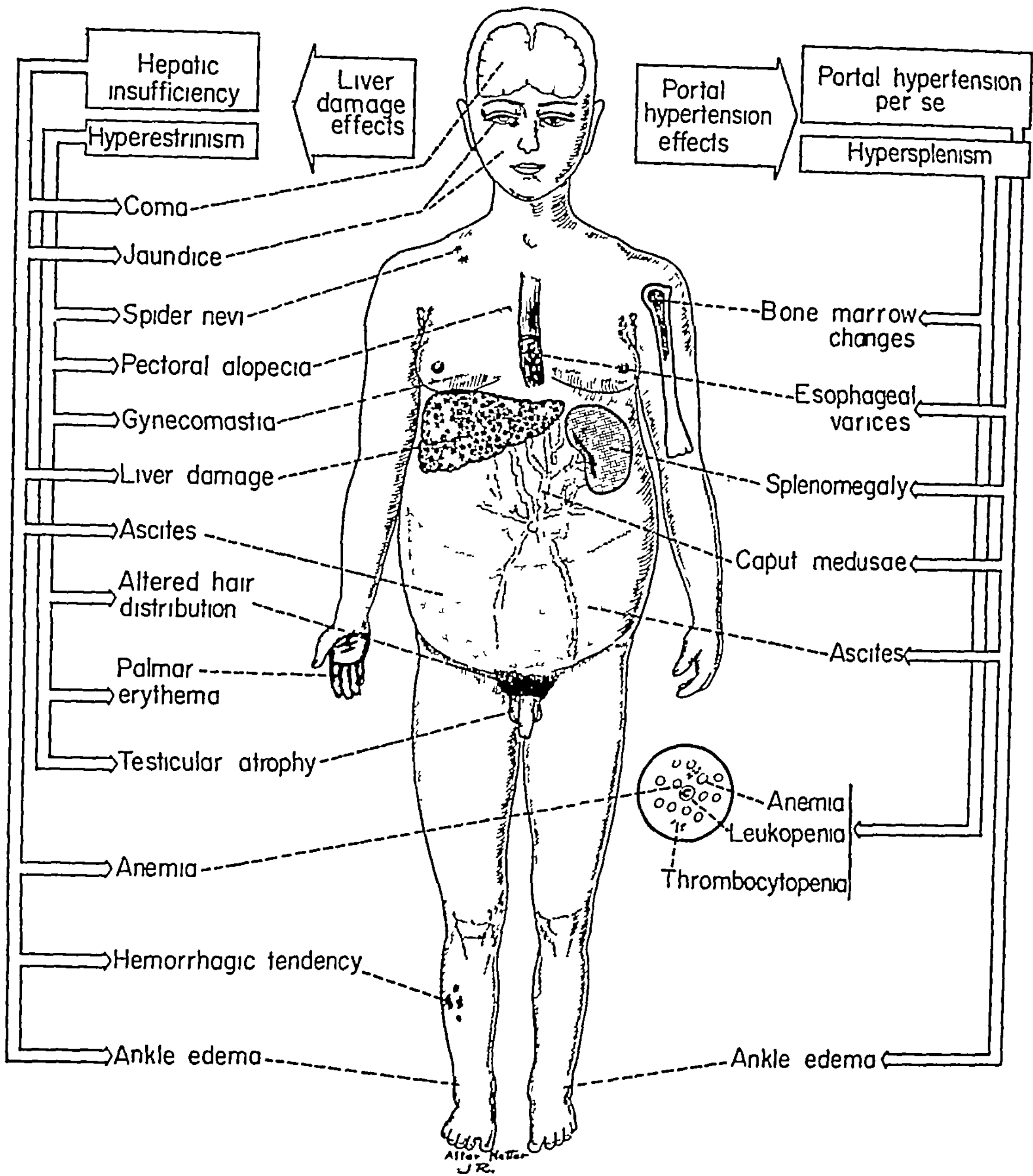


Fig 80 Pathophysiology of portal cirrhosis This informative diagram constructed by Netter clearly describes the manifold physiologic effects produced by hepatic cirrhosis (From Netter, F H, *The Ciba Collection of Medical Illustrations*, Part III, Vol 3, Summit, N J Ciba Pharmaceutical Products, Inc, 1957)

was noted previously that the liver parenchyma tolerates complete common duct obstruction for several weeks without significant impairment in liver function, in contrast, the insult of anesthesia-operation in the patient with severe hepatocellular injury may prove fatal

The stools should be inspected daily The total serum bilirubin level should be rechecked every 3 or 4 days and the other liver function tests repeated weekly If some bile was initially present in the stools but then is consistently absent, the first impression in the elderly patient might be tumor (Fig 77) and the second, common duct stone —unless collateral evidence indicates otherwise Again, whereas hepatitis may be associated with acholic stools, the stools are rarely completely acholic (grayish white) consistently (Fig 78) With common duct stone there may be intermittent escape of bile past the stone, with some degree of intermittent color in the stool, of course, in some patients with stone the biliary metabolism is normal between attacks, jaundice is absent, and the stools are normal in color

Intermittent appearance of bile in the stools is rare in patients whose obstruction is the result of malignancy

Punch biopsy of the liver may be helpful in diagnosis and, considering the frequency with which the procedure is performed, complications are few

Diagnostic laparotomy may be necessary to exclude surgical jaundice in the occasional patient in whom a satisfactorily definite diagnosis cannot be achieved by other means. However, with proper care and judicious delay for a week or so, such cases need not be too frequent. Moreover, by waiting a suitable period the more fulminating cases of hepatitis will be excluded, patients with other types of medical jaundice do not constitute such formidable operative risks. If no extrahepatic biliary obstruction is found at exploratory laparotomy, including operative cholangiography where indicated, an adequate liver biopsy should be taken.

Bile Peritonitis

Since even in acute cholecystitis no microorganisms may be cultured from the bile, the escape of bile into the free peritoneal cavity produces a primarily chemical rather than bacterial peritonitis, at least initially The attendant ascites due to chemical inflammation may seriously deplete the extracellular space of water and electrolytes Later infection may play an increasingly important rôle in this condition The absorption of bile from the peritoneal cavity results in jaundice Unless drainage is established to the outside, the resulting "toxemia" may prove fatal Fortunately, in many instances the site of gallbladder perforation is promptly sealed off by omentum.

That instances of gallbladder rupture and bile peritonitis need not be fatal is well exemplified by patients who at operation exhibit multiple gallstones immobilized in widely scattered areas of the omentum by mature fibrous tissue in addition to clusters of stones lying in the immediate vicinity of the chronically diseased—but not currently perforated—organ (Fig 84)

Portal Hypertension: Surgical Problem in a Medical Disease

Elevation of portal venous pressure may be due to suprahepatic causes (constrictive pericarditis, tricuspid valve incompetence, and thrombosis of the hepatic veins or Chiari's syndrome), intrahepatic causes (principally various forms of cirrhosis), and infrahepatic causes (portal vein thrombosis) Chiari's syndrome and the intrahepatic and infrahepatic causes are managed by intra abdominal anastomoses between elements of the portal and caval venous systems

MECHANISM OF PORTAL HYPERTENSION *Normal hepatic blood flow* The blood flow through the normal human liver has been estimated by measurement to average approximately 1500 cc. per minute, with a range of 1000 to 2000 cc per minute. About 75 per cent of this blood reaches the liver through the portal vein and the other 25 per cent is supplied by the hepatic artery (Fig. 74) However, the arterial blood may carry as much as 50 per cent of the oxygen supply Both clinical and experimental evidence indicates that the portal blood is not homogenously mixed but that it is channeled in streams. Blood from the splenic, gastric and inferior mesenteric veins is carried principally to the left hepatic lobe whereas blood from the small bowel (containing absorption products) and the right colon flows through the superior mesenteric vein to be delivered preponderantly to the right hepatic lobe. This channeling of the blood may account for the fact that amebic abcess is more frequent in the right than in the left lobe of the liver, the cecum being a source of these parasites The distribution of metastases from the splanchnic organs is somewhat affected by venous channeling but hepatic metastases are often so profuse that any slight difference pertaining to the right and left hepatic lobes is obscured

The splenic artery contributes approximately one fourth to two-fifths of the portal flow through the liver (Fig. 75) *via* the portal vein

ics and intravenous serum albumin are helpful in some patients

Portacaval shunt has been employed in the treatment of ascites in the occasional patient, as has splenectomy, but by and large these and other surgical measures ("rectus wick" procedure, omentopexy, etc) have been of little benefit Actually, the presence of significant ascites is often taken as a contraindication to portacaval shunt, even following bleeding from esophageal varices

Hypersplenism In addition to the vascular alterations (or, more specifically, as a result of these) the spleen becomes engorged and the condition referred to as secondary (to portal hypertension) hypersplenism may develop It is manifested by a reduction in platelets, neutrophils, and red cells, alone or in combination Although the specific mechanism of this condition is obscure, it has been suggested that blood stasis in the spleen permits longer contact with the splenic sinusoids, and that the normal processes of blood cell regulation are allowed to destroy excessive numbers of cells Following splenectomy the condition may improve

PORTACAVAL SHUNT FOR PORTAL HYPERTENSION In 1945 Whipple[25] reviewed the problem of portal hypertension and bleeding esophageal varices, and presented his experience with portacaval and splenorenal shunts in the management of this condition He noted that the Russian physiologist Eck had published his report on "The Ligature of the Portal Vein" as early as 1877 and had even then suggested that the fistula might be used to sidetrack obstruction of the portal vein Nevertheless, it was not until the early 1900's that successful operations were reported in man Since Whipple's initial report of his clinical experiences with portacaval shunt the procedure has had a wide clinical trial

When to use a venous shunting procedure One is forced at least to consider a shunting operation when a patient suspected of having portal hypertension exhibits hematemesis or melena The individual may or may not have previously been known to h liver disease However, the possibility esophageal bleeding should be entertai in all patients who exhibit hematemesis, pecially if hemorrhoids and other stigm of portal hypertension are present O esophageal varices are thought of, the ra ologist is asked to search for these lesio esophagoscopy may be required in so instances In brief, while upper gastro testinal hemorrhage may be due to e phageal varices, the mere presence of su varices does not establish that they are source of hemorrhage, for a peptic ul may be bleeding Still, in 200 patients w Laennec's cirrhosis reviewed by Famer a Halsted,[10] 38 per cent exhibited hemorrha from the upper alimentary tract Esopha eal and gastric varices were the source bleeding in 59 2 and 2 6 per cent respe tively, and peptic ulcer and gastric erosio were the source of bleeding in 18 4 and per cent respectively In 22 patients (or per cent of those in whom hemorrhage o curred) two or more lesions of the upper a mentary tract were demonstrated, both pe tic ulcer and esophageal varices were prese in 12 of these 22 patients In a series of 12 consecutive autopsies, peptic ulcer was pre ent in a significantly greater number of pa tients with cirrhosis than in patients witho cirrhosis

Obviously, then, as always, it is advisab to establish an accurate diagnosis preo eratively, where possible

One might caution against so-calle "emergency portacaval shunt" in patient in whom the bleeding continues uncontrolle with one of the various esophageal hydro static bags Our experience with such pa tients has been limited, but the results hav been quite poor We currently believe tha the chance for survival in such an individua is as good with continued esophageal tam ponade and transfusion as it is with an emer gency shunt procedure In contrast, th transesophageal suture of bleeding varice is a much simpler and far more rapid emer-

gency procedure Yet it too can be disappointing

Which shunt procedure should be employed? Let us assume that the presence of portal hypertension has been reasonably well established on the basis of a palpable spleen and venous enlargement (esophageal hemorrhoidal, epigastric and other vessels) Moreover, depressed liver function values and other collateral evidence may also suggest that cirrhosis is causing the intrahepatic block (If liver tests are normal extrahepatic block is suggested) What operation should be done (Fig 75)?

The operation selected will depend upon the level of the venous obstruction Again intrahepatic block may be due to portal cirrhosis or to thrombosis of the hepatic veins (Chiari s syndrome) Extrahepatic block may be congenital or the result of thrombosis of the portal vein or of one or more of its tributaries Or a combination of the two main types may occur If obstruction is intrahepatic diversion of flow from the portal vein or any of its tributaries may be satisfactory but if the obstruction is extrahepatic it will be necessary to select a member of the splenoportal system whose junction with the splenoportal vein is distal to the point of obstruction Here a splenorenal anastomosis may be required

Percutaneous splenic portal venograms have proved to be safe and most helpful Whereas formerly one might spend literally hours at laparotomy searching for a suitable branch of the portal vein with which to perform the anastomosis now it is possible to demonstrate preoperatively the presence or absence of portal vein obstruction by injecting a radiopaque medium (Urokon, for example) into the spleen and recording with roentgenography the movement of the material from the splenic pulp through the portal venous system. An example is presented in Figure 81 marked dilatation of the vessels of the portal system including esophageal collaterals was demonstrated

At operation one usually finds that an end of portal vein to side of vena cava anastomosis is more easily and safely achieved than is side-to side anastomosis of these two large vessels The dilated portal vein may be almost an inch in diameter as it enters the liver and considerable tension may be required to effect side to-side apposition of these vessels

While the splenorenal shunt does not lower the portal pressure as satisfactorily as does the portacaval shunt—and while the former fistula is more likely to thrombose than the latter—the splenorenal shunt may represent a judicious compromise in patients with borderline hepatic reserve Patients with a portacaval shunt are more susceptible to postoperative liver failure than are those with the lesser shunt

At the time a shunt is performed the spleen should be removed This would naturally be done in the course of the splenorenal shunt but it probably should also be done in association with portacaval shunt In one case the portacaval shunt effected a lowering of the portal venous pressure from an initial level of almost 400 mm. H_2O to 300 mm H_2O, but splenectomy reduced the pressure still further to approximately 200 mm. H_2O

Results of portacaval and splenorenal shunts There has been considerable contradiction in the literature regarding the long range value of these operations To begin with the underlying hepatic disease is usually not improved by the procedure in fact, liver function tests may show further impairment Therefore, the operation is a purely palliative one employed to control hemorrhage that threatens exsanguination It is on this basis that its value must be assessed

Linton and his associates[9] reported their results in 129 patients operated upon over a period of 10 years, all but 6 of whom had bled massively from esophageal varices Portal hypertension was on the basis of cirrhosis in 100 patients and secondary to extrahepatic portal bed block (so-called Banti s syndrome) in 29 There were 83 splenore



Fig 81 Above Splenoportagram in portal hypertension The contrast medium was injected percutaneously into the spleen (by Dr Robert D Sloan) At operation 2 hours later the point of entry of the needle into the spleen could not be identified *Below* The cirrhotic liver is seen in the left foreground and, beyond the stomach, the large lobulated spleen in the background This 19-year-old girl had hypersplenism secondary to portal hypertension Splenectomy reduced the portal pressure and improved the peripheral blood picture She had had no esophageal bleeding or ascites The cause of the cirrhosis was not determined

shift" shunts, and there were 16 unsuccessful attempts to construct a shunt Serious operative or postoperative complications directly related to the liver occurred in 27 (19 per cent) of the operations Frank liver failure developed in 22 patients, 8 of whom died Five patients died during surgery of uncontrollable venous and capillary bleeding All 5 of these occurred in the first 5 years of the study (1945 to 1949) before the use of fresh blood became routine during shunt surgery A preoperative Bromsulphalein retention of 10 per cent or less gave a virtual guarantee from postoperative liver complications

Conversely, a low serum albumin level preoperatively (below 3 0 gm per 100 ml) was associated with a prohibitively high (66 per cent) rate of hepatic complications The choice of operation was an important factor in the outcome, for postoperative liver failure occurred twice as often after a portacaval shunt than after splenorenal anastomosis The over all mortality was approximately 30 per cent, and the operative mortality was approximately 10 per cent

Linton and his associates believe that shunt surgery can be performed in patients with serious liver disease at a reasonable risk, and that such surgery can relieve portal hypertension and markedly reduce the occurrence of bleeding from esophageal varices thereby lengthening the survival of these patients and in the majority improving the state of health. Liver function as measured by the usual tests, is not materially improved in most patients but the hazard of esophageal hemorrhage is diminished

These results are reasonably typical of the "favorable' series reported, including those of Blakemore[2] In contrast adverse reports are becoming more frequent, derived from a variety of approaches Following a review of the reported experience in conjunction with an analysis of the cases of cirrhosis encountered at the San Francisco Hospital Cohn[5] concluded that (1) many cirrhotics who bleed do not bleed from esophageal varices, (2) close scrutiny of the results reported in the literature makes it reasonable to question whether the operations advocated are really responsible for the good results obtained, (3) operative treatment is justified in only a highly selected group of cirrhotics

Ripstein[22] in reviewing 30 cases, concluded that portacaval shunts appear to be of doubtful value and produce at best a temporary benefit. He considered that even partial deviation of the portal flow may impair liver function.

Preshaw and his co workers[20] obtained evidence in dogs that portacaval shunt diminished liver tolerance for carbon tetrachloride poisoning as reflected in changes in bromsulphalein retention. Not unexpectedly, Bradley and his associates[4] found that portacaval anastomosis reduced hepatic blood flow

Finally, Palmer[19] measured esophageal venous pressure at esophagoscopy and found no good correlation between the size of the esophageal varices and venous pressure. It has been suggested that, in addition to increased intraluminal pressure, hemorrhage from esophageal varices may be the result of trauma or of mucosal ulceration

HEPATIC ARTERY LIGATION FOR PORTAL HYPERTENSION This procedure enjoyed a brief notoriety, but has now been virtually abandoned

The Gallbladder and Biliary Tract

Functions of the Gallbladder

The human gallbladder normally has a capacity of approximately 50 cc of bile but, owing to the concentrating powers of this organ, this amount of bile may represent the organic material from as much as 300 to 500 cc of liver bile This reservoir function permits storage of the active bile components during fasting to be discharged into the duodenum to aid digestion when food material in the duodenum stimulates the release of the motor hormonal substance *cholecystokinin* This concentrating power of the gallbladder, that of water absorption is the basis of gallbladder visualization on cholecystogram.

MOTOR FUNCTIONS OF THE GALLBLADDER. The gallbladder appears to be subject to two types of contractions, one is a rather weak type of contraction at irregular intervals, and the other is a strong type of tonic contraction of the organ as a whole. The motor activity of this organ is affected by both chemical and nervous influences. During the fasting period the tone of the sphincter of Oddi rises so that it can resist the pressure of approximately 300 mm. of bile The liver continues to secrete bile during the fasting period, and when the pressure in the distending bile duct rises to about 70 mm. of

H_2O the bile begins to flow into the gallbladder, where it is concentrated Following a meal, however, the sphincter of Oddi presents less resistance and now allows bile to flow through at a pressure of about 100 mm of bile If the meal contains a considerable amount of fat, the elaboration of cholecystokinin in the mucosa of the duodenum is especially stimulated This hormonal substance exerts a marked effect upon the musculature of the gallbladder, and the organ may be rapidly emptied of its contents at a pressure of some 200 mm of bile

If the pressure in the bile passages rises to a point much above 300 mm of bile, as it eventually does in complete common duct obstruction, the secretion of bile by the liver will cease and the patient becomes jaundiced That is to say, the secretory pressure of the liver cells is approximately 300 mm of water, as noted previously

THE CHOLECYSTOGRAM The ability of the gallbladder to concentrate bile is the basis of the Graham-Cole test, the cholecystogram When a suitable compound containing iodine is given by mouth or intravenously, it is excreted by the liver cells and passes into the gallbladder, where the dye is concentrated by the absorption of water, rendering the filled gallbladder opaque on roentgen examination It is now often possible, even in the absence of the gallbladder with its concentrating power, to visualize the bile ducts by means of the intravenous injection of Cholografin[11]

If one can be certain that the patient took and retained the iodine-containing compound used for cholecystogram—and if he did, some of the unabsorbed material can usually be visualized in the bowel—various conclusions may be drawn, depending upon the findings First, translucent stones may be visualized as filling defects in the opaque medium filled gallbladder Second, the gallbladder may not be visualized, usually an indication that cystic duct obstruction exists, presumably due to stones, if a second study confirms this result, exploration is justified, if otherwise indicated Third, the wall of the gallbladder may be so diseased that only slight concentration occurs but, even so, any stones present are usually visualized If the gallbladder satisfactorily concentrates the medium and then empt promptly upon the ingestion of cream some other fat, and if no stones are seen, th the organ is assumed to be essentially no mal Of course, gallstones may be rac opaque and demonstrable on a plain film the abdomen in from 10 to 15 per cent cases

DUODENAL DRAINAGE Another function te that may indicate the presence of gallston is that of the microscopic examination duodenal drainage material for cholester or calcium bilirubinate crystals A tube passed through the stomach and into th duodenum opposite the papilla of Vater an bile is collected which at first will be a ligh yellow color, referred to as "A" bile, th portion comes from the liver Olive oil c magnesium sulfate is then injected throug the tube, and this acts to stimulate the for mation and release of cholecystokinin, whic causes a vigorous contraction of the gall bladder and forces gallbladder bile throug the common duct and into the duodenum This bile from the gallbladder is greenish in color and more viscid, and is called "B" bile In either of the specimens, but particularly in the "B" bile, cholesterol or calcium bilirubinate crystals may be seen microscopically The presence of such crystals is considered to represent strong evidence of the presence of gallstones However, while this test is helpful, most gallstones are now more easily diagnosed by the use of the history and the cholecystogram, and duodenal drainage is little used

DRUGS AND THE SPHINCTER OF ODDI It has long been appreciated that amyl nitrite and nitroglycerine may relieve gallbladder colic This is due to the fact that they relieve the spasm of the sphincter, while atropine and pilocarpine do not Morphine and other opiates cause spasm of the sphincter, reflected in various clinical measurements of bile duct pressures and in the rise in serum amylase

that is often observed Denervation of the sphincter region has been advocated to relieve spasm, but various autonomic studies have not clearly demonstrated a consistent nervous influence over the sphincter in man

ETIOLOGY OF GALLSTONES The mechanism by which the various types of gallstones are formed is still not settled The ratio of bile salts to cholesterol has always been considered to be important in the genesis of stones since the presence of bile salts increases the concentration of cholesterol which can be present in gallbladder bile without precipitation The small dark stones that form even in children in hemolytic anemia indicate that increased amounts of pigment may play a rôle in such instances. The relation of the diet to the formation of gall stones has not been clarified in human beings A high cholesterol intake which leads to an increase in its concentration in the bile may explain the frequency with which obese patients have cholesterol gallstones. Pregnancy[23] appears to be a predisposing factor Pure calcium gallstones or calcium enclosed cholesterol stones are usually associated with a history of inflammation

Cholesterol and calcium bilirubinate stones comprise the majority of calculi but others consist of calcium carbonate and calcium oxalate

Acute Cholecystitis

Acute cholecystitis usually represents an acute flare up of chronic calculous cholecystitis The mechanism of the intermittent recrudescence of this chronic condition is often that of acute cystic duct obstruction by an impacted stone The inflammation associated with the acute exacerbation is due to chemical rather than bacterial agents since cultures taken from even severely inflamed organs rarely reveal significant bacteria However this is not to say that infection may not in time be superimposed upon the chemical cholecystitis

The mechanism of many attacks of cholecystitis is presented in Figure 82 The colic associated with the acute attack is due to

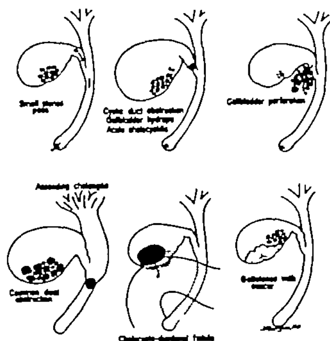


Fig 82 The mechanisms of gallstone formation are debated, but many contributing factors are known (see text) Acute cholecystitis is caused by chemical inflammation rather than by bacteria Gallstone colic is usually produced by intermittent obstruction of the cystic duct

obstruction of the neck of the cystic duct with consequent and painful distention of the gallbladder or to spasmodic contraction of the organ and particularly the infundibular region Obstruction of the cystic duct may result in much enlargement of the gall bladder due to both edema fluid and mucus from the lining cells The mucosal cells normally secrete approximately 20 cc each 24 hours, and one need not postulate a ball valve effect with bile entering the organ but not being discharged to account for the hydrops or ' empyema.

The obstructing stone may, in addition to colic and surrounding inflammatory edema produce actual pressure necrosis of a portion of the wall of the organ resulting in perforation (Fig 82) Fortunately, the site of impending rupture is usually sealed off promptly by omentum. The dislodgement of the obstructing stone forward or backward often relieves the attack.

PAIN DISTRIBUTION IN GALLBLADDER COLIC The pain of biliary colic whether from the gallbladder or from the common bile duct,

is typically referred to the right upper quadrant and, less frequently, posteriorly to a point between the scapulae Cole[6] found that of 211 consecutive patients having cholecystectomy, 45 6 per cent had pain only in the right upper quadrant Pain was located in the epigastrium alone in 27 2 per cent and in the epigastrium as well as the right upper quadrant in 18 9 per cent In 5 3 per cent of the subjects the pain was located elsewhere, including the left upper abdominal quadrant and the precordium It was emphasized that while the pain of cholecystitis could be referred to areas other than the upper right quadrant, this happens only occasionally, and that the clinician must be cautious in blaming the gallbladder for such symptoms Although at autopsy approximately 32 per cent of women and 16 per cent of men past the age of 40 have gallstones,[23] less than one-third of patients with gallstones have symptoms This further underscores the need for careful evaluation of the patient for further lesions even though biliary calculi have been demonstrated on roentgenogram

The pain of gallbladder disease may be intermittent or it may be sustained for days Generally it is of a short duration and may last less than 1 hour in about 50 per cent of the patients Characteristically the pain occurs in attacks, and does not continue as a constant distress over a period of several days unless empyema or some other complication has occurred One finding which is fairly common is that the patient will have residual tenderness in the right upper quadrant for from 24 to 48 hours following the actual pain of the gallbladder attack

Very occasionally the pain of gallbladder colic will be referred to the precordium and even rarely may extend down the left arm In such a case it is much wiser to take the conservative view that such pain, even in the presence of gallstones, is due to myocardial ischemia Nevertheless, when proper caution has been exercised, an evaluation of the total case may suggest removal of the gallstones anyway, which may at times relieve the "anginal" pain It has been s that distention of the gallbladder or c common bile duct can cause precordial in persons who have no demonstrable diac disease However, Hodge and hi sociates[13] studied animals and found distention of the biliary tract failed to duce significant changes in the electroca gram without a pre-existing lesion o myocardium, when one or more of the onary arteries had been ligated, diste of the biliary tract in dogs did produ abnormal electrocardiogram

INNERVATION OF THE GALLBLADDER RÔLE IN CHOLECYSTITIS The pain of c cystitis is mediated largely by the sy thetics (Fig 258) Patients who have bilateral thoracolumbar sympathect may experience acute cholecystitis w goes on to perforation without having at any time, less commonly this may o following right sympathectomy only lack of sensation of course constitutes a uine hazard following extensive sympat tomy

While aware of the importance of mec ical and chemical factors in the etiol of acute cholecystitis—involving as they the obstruction of the cystic duct and rangements in bile constituents—How Milford, and De Bakey[14] examined significance of the nervous mechanism in pathogenesis and progression of this dise Previously, Eastwood and Womack[8] had dicated the extent to which the nerve sup of the gallbladder might be involved in flammatory lesions of this organ, as l Bonnet[3] earlier The pain of acute ch cystitis had been successfully treated splanchnic block on the right side or, wh necessary, bilaterally Howard and his sociates studied the effect of sympathecto on the pathogenesis of cholecystitis in do and they concluded that sympathetic nervation of the gallbladder and the bili tract in the dog had a significant effect up the inflammatory process in experimen acute cholecystitis produced by ligation the cystic duct and the introduction of b

salts into the gallbladder Whereas in the control series only 15 per cent of the animals had a normal gallbladder following this procedure, in the animals having a simultaneous right sympathetic denervation this figure was 57 per cent and in those with bilateral denervation it was 75 per cent. It was suggested that the blocking of impulses arising from the stimulating action of the chemical distortion of the bile upon the nerve endings, along with the abolition of the autonomic reflexes had produced a beneficial effect upon smooth muscle spasm and vasoconstriction this retarded the progression of the inflammatory process itself The relationship of gallbladder innervation to acute cholecystitis in the patient is of course open to speculation but these studies do emphasize the intimate relationship which the innervation bears to certain aspects of this disease For one thing if right-sided thoracolumbar sympathectomy is to be performed it is advisable to examine the gallbladder and to remove any stones that are found at that time or perhaps better, to remove the organ

The rôle of *vagal or parasympathetic innervation* of the gallbladder is less definitely established. The effect of double vagotomy on the motor activity of the human gallbladder was studied by Johnson and Boyden[16] and satisfactory cholecystograms were obtained in 11 out of 13 male patients studied over a 3-year period before and after vagotomy for peptic ulcer In one group, consisting of 5 patients in whom vagotomy was incomplete as revealed by the Hollander insulin gastric secretion test, there was a continued rapid evacuation of the gallbladder which is said to be characteristic of peptic ulcer patients In the second group, consisting of 6 patients in whom the vagotomy was initially complete, the rate of emptying of the gallbladder was significantly retarded but the rate was not less than that of normal individuals of corresponding sex and age *It was concluded that* the vagi are not essential to the evacuation of the human gallbladder (in contrast to the findings in laboratory animals) and that emptying of the gallbladder is regulated primarily through the hormonal mechanism involving cholecystokinin It was noted, however, that in the 6 patients in whom the vagotomies were complete, the fasting volume of the gallbladder was approximately doubled after vagotomy It was believed that this was due to the loss of vagal fibers which normally maintain the tonus of the gallbladder during interdigestive periods This tonus failing, the gallbladder was unable to resist the influx of liver bile as efficiently as before and hence progressively enlarged Johnson and Boyden raised the question as to whether such enlargement might not lead to gallbladder pathology

MANAGEMENT OF ACUTE CHOLECYSTITIS Whereas 20 years ago many surgeons preferred merely to remove the stones and to drain the acutely inflamed gallbladder, where surgery was felt to be absolutely necessary during the acute attack (any operation being postponed where possible), the trend in the last decade has been to perform a cholecystectomy far more frequently as an emergency procedure Certainly these patients do well postoperatively following successful surgery If the structures are not amenable to careful dissection, because of a dense inflammatory process, then cholecystectomy should be postponed and the gallbladder simply evacuated and drained. Indeed, in some elderly patients a single large stone may be removed and no further surgery required. In summary the single most important consideration which should settle the issue between cholecystectomy and cholecystostomy in the presence of acute inflammation is the question of whether or not accurate dissection in the area of the common duct can be accomplished, for without this exposure the risk of a life-shortening common duct injury is too great

If the attack of acute cholecystitis or of acute recrudescence of chronic cholecystitis *is not severe* one may well proceed with conservative management and operate electively after diagnostic studies On the other

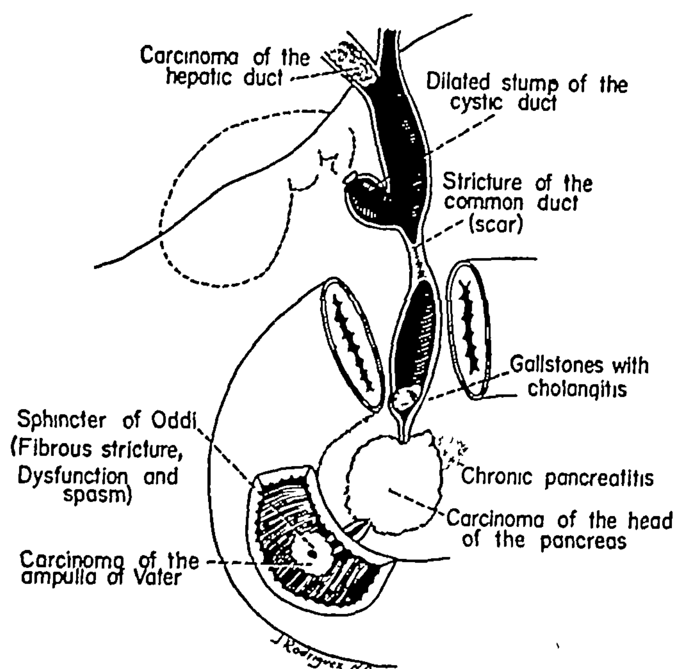


Fig 83 The total clinical examination of the patient is far superior to laboratory tests in the diagnosis of lesions of the bile passages However, judiciously used tests materially supplement the information gained through clinical means

hand, if the patient is becoming worse, operation may be imperative As a rule of thumb, purely for guidance, it is our practice to operate if the white cell count rises above 15,000, or if the pulse rate is above 100, or if the oral temperature is above 102°, or if right upper quadrant pain and tenderness persists unduly or grows more severe—and always if the over-all clinical picture does not progress satisfactorily Again, it is to be remembered that gallbladder attacks are relatively brief in duration unless some complication has occurred Among the complications that may be anticipated are hydrops or empyema of the organ, perforation, jaundice due to encroachment of the inflammatory pressure on the common duct, cholecystoenteric fistula and pancreatitis

Carcinoma of the gallbladder is usually associated with stones (Fig 84)

Common Bile Duct Obstruction

Several causes of common duct obstruction are shown in Figure 83 Of these, by far the most important are common duct stone, carcinoma of the head of the pancreas or the ampulla, and postoperative stricture Chronic or even acute pancreatitis may also produce obstructive jaundice, as may types of hepatitis at certain stages

The differential diagnosis among these several conditions is made on the basis of history and physical examination, roentgen studies (not often very helpful), and liver function studies—where a definite diagnosis can be made preoperatively, which is by no means always possible This has been discussed previously (p 230) The primary problem is to determine whether the jaundice is medical or surgical in nature, that is, whether it is due to hepatitis in which no operation is indicated or to actual mechanical obstruction which will be relieved only by surgery in most instances

WHITE BILE This is the name applied to the material found in the gallbladder after prolonged cystic duct obstruction, or in the common bile duct in the presence of longstanding common duct obstruction In the case of the gallbladder, this material consists largely of mucus In common duct obstruction, however, its significance lies in the fact that the liver has ceased secreting bile pigment, and that the patient is suffering from almost or complete hepatic secretory suppression In such a case the colorless contents of the ducts are largely derived from the ductal mucosa, and it is surprising the extent to which the biliary tree may be dilated and filled with such material The author recalls one instance in which, when in the presence of longstanding postoperative stricture of the common bile duct the greatly dilated common hepatic duct was opened, such a quantity of white bile poured forth that the dilated intrahepatic ducts were permitted to collapse and the liver diminished visibly in size This marked dilatation of the intrahepatic ducts can reduce considerably the volume of functional liver tissue, as noted previously

Regardless of the precise origin of the white bile, whether from the mucosa or by some increment of secretion by the liver of a bile with a low pigment content, or both,



Fig 84 Above Gallstones in the omentum from previous gallbladder rupture The stones had been surrounded by thin fibrous adhesions *Below* Associated gallbladder carcinoma and gallstones in the patient shown above Although gallstones are common whereas gallbladder carcinoma is not the latter is found associated with gallstones in a high percentage of cases

the presence of white bile usually denotes prolonged obstruction of the extrahepatic biliary tree

Ravdin and his associates[21] found that there was a marked reduction in concentration or even an absence of bile salts in common duct drainage after the release of common duct obstruction. The interval between the release of obstruction and the reappearance of the bile salts was proportional to the degree of cholangitis associated with the rate of return of normal liver activity In biliary fistulas with diversion of bile from the intestinal tract the loss of bile salts may be more important than the loss of base or chloride

Biliary Dyskinesia—the Postcholecystectomy Syndrome

Postcholecystectomy colic or biliary dyskinesia is a poorly defined syndrome which tends to occur in nervous and hypersensitive persons and which can be diagnosed only by the exclusion of organic disease The cause of the dyskinesia in most cases has not been clearly established but it is thought that spasm of the sphincter of Oddi plays a part in the production of these symptoms Actually, failure of cholecystectomy to abolish all symptoms or the occurrence of a different type of pain and discomfort following cholecystectomy, may be due to a variety of causes, as shown in Figure 83 Among these are a dilated stump of the

cystic duct, a stricture of the common bile duct, a residual stone in the common bile duct, chronic pancreatitis with scarring, and disease of the sphincter of Oddi and ampullary region The disease of the sphincter may be a functional or neurogenic process, or it may consist of fibrosis with fibrotic narrowing of the opening of the ampulla Of course, one must also exclude the possibility that disease outside the biliary tract may be the cause of the symptoms, among such conditions being peptic ulcer, hiatal hernia, pancreatitis, overlooked malignancy, or psychoneurosis from any cause Cole[6] suggested that paravertebral sympathetic nerve injection with procaine be compared with the relief afforded by isotonic saline injection, in differentiating "psychogenic" from "organic" pain.

We do not feel qualified to offer a suggestion as to how often disease of the sphincter is present, but we did encounter dense fibrotic stricture of the sphincter in one patient with relapsing pancreatitis

Without question, sphincterotomy (Fig 92) is being rather frequently employed by many American surgeons, and its value in "biliary dyskinesia" and pancreatitis will ultimately be decided Incidentally, Cole and Grove[7] found that chronic pancreatitis was the cause of benign stricture of the common duct in 8 6 per cent of 92 patients with common duct stricture reported by them

STRICTURE OF THE COMMON BILE DUCT. FURTHER COMMENT This condition has been referred to only briefly, but it is one of the most serious complications affecting the hepatobiliary system Although occasional cases are due to pancreatitis or to infection rather than to operative damage, the overwhelming majority of cases of acquired stricture of the common duct are the result of injury at operation

Jaundice is the principal finding This may occur almost immediately or it may not appear for months *Injury to the common duct may be associated with a profuse flow of bile from the wound in the immediate postoperative period,* followed by jaundice when and if the flow of bile diminishes Of co if there is a T-tube in the common above the site of injury, then the pa will not become jaundiced until the T is removed The difficult diagnostic p particularly when there has not been fuse bile drainage following operation. differentiating the common duct injury common duct stone The recent availal of Cholografin, with which the common may be outlined by the intravenous injec of proper amounts, may make this diffe tial diagnosis less difficult Actually, h ever, the history of the events at opera and the patient's subsequent course re the diagnosis of probable common duc jury an easy one to establish in most ca

If the obstruction is not relieved, the sistent jaundice, usually associated varying degrees of cholangitis, will pro progressive liver damage Whatever the eration used, it must be accepted tha most instances the lifespan of the patient be shortened, for on admission most of t individuals have had already a serie various types of operations in an effor restore and maintain continuity of hepatointestinal connection The restora of end-to-end continuity of the common d offers the best chance of lasting success fortunately, permanently successful rec structions are far less frequent than repo *results would lead one to believe*

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Chapter 12

The Pancreas

Surgical Anatomy

The anatomic relationships of the pancreas are shown in Figure 85, and at operation the positions of the duodenum, common bile duct, pancreatic ducts, and mesenteric vessels are of particular importance The splenic artery courses just beneath the superior margin of the pancreas, and this can afford an important approach to controlling hemorrhage at splenectomy The left adrenal gland lies beneath the tail of the pancreas, and is readily approached by incising the peritoneum along the inferior border of the pancreas and retracting this organ anteriorly and superiorly (Fig 10) Pancreatic injury may occur in operations upon the stomach or the other surrounding organs Pancreatitis may result in jejunal obstruction at the ligament of Treitz

Functionally, the fact that the main pancreatic duct and the common bile duct enter the duodenum through a common channel (the ampulla) in approximately two-thirds of the cases has provided the most durable theory regarding the etiology of pancreatitis, namely, that the bile regurgitates into the pancreatic ducts and activates pancreatic enzymes which digest surrounding tissues However, this concept is being modified

The *blood supply* of the pancreas is derived from the superior and inferior pancreaticoduodenal arteries, the splenic artery, and branches of the hepatic artery The lymphatic drainage is rich and enters the pancreaticoduodenal, preaortic, and celiac nodes There may also be lymphatic connections with the gallbladder, stoma and spleen

The nerve supply of the pancreas is sho in Figure 86 The sensory or afferent ne supply appears to reside largely in the sy pathetic system, the pain from pancreati can usually be relieved by division or blo of the splanchnic nerves on the right, thou a bilateral procedure is necessary in so patients In clinical observations, Bliss a associates[2] found that pain originating fr the head of the pancreas localized in t epigastrium to the right of the midlin was mediated by the right splanchni through the right thoracic sympathet ganglia 6–11, and that it could be relieve by the interruption of these afferent path ways Pain arising from the body of th pancreas localized in the mid-epigastrium was mediated by the splanchnics throug the thoracic sympathetic ganglia 6-11 bi laterally, and could be abolished by bilatera interruption of these afferent pathways Pain from the tail of the pancreas was localized in the epigastrium, was mediated by the left splanchnics through the sympathetic ganglia T–6 through L–1, and could be relieved by interruption of these afferent pathways There were occasional exceptions to the above findings, however, and it was suggested that bilateral sympathectomy may be necessary to obtain permanent relief from segmental involvement of the pancreas in some patients Pancreatic pain radiates also to the back

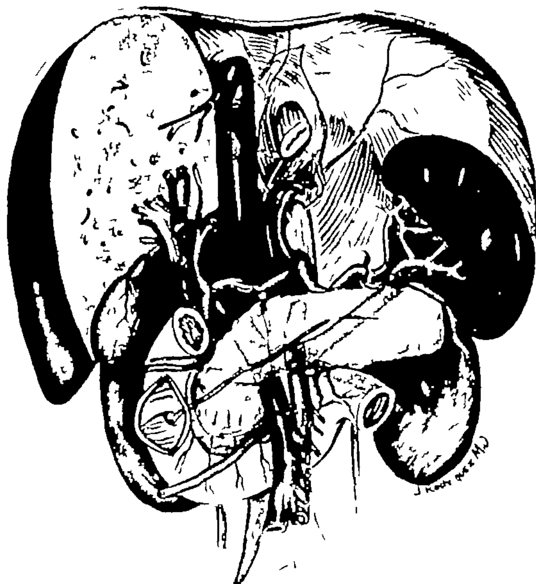


Fig 86 The topography of the pancreas The management of surgical lesions of the pan creas is rendered difficult because of the anatomic physiologic and roentgenologic inaccessibility of the organ (From HARDY J D AND BOWLIN J W Some complications of pan creatic disease Illustrative cases with notes on management Ann Surg 145: 818 1957)

The External (Exocrine) Secretion of the Pancreas and Its Nervous and Humoral Control

Pancreatic Juice Composition

The pancreas secretes from 1 to 2 L of alkaline fluid per 24 hours and the ionic constituents of this material are shown in Figure 28 Note that the sodium bicarbonate content is relatively high The principal enzymes of the pancreatic juice are trypsin which is a powerful proteolytic enzyme, lipase, which splits neutral fats, and amylase which splits starch to maltose The activity of lipase in splitting neutral fats into diglycerides, monoglycerides, and free fatty acids and glycerol is markedly increased by the activity of bile Trypsin breaks down polypeptides and may even eventually produce amino acids The juice collected directly from the pancreatic duct without allowing conta-

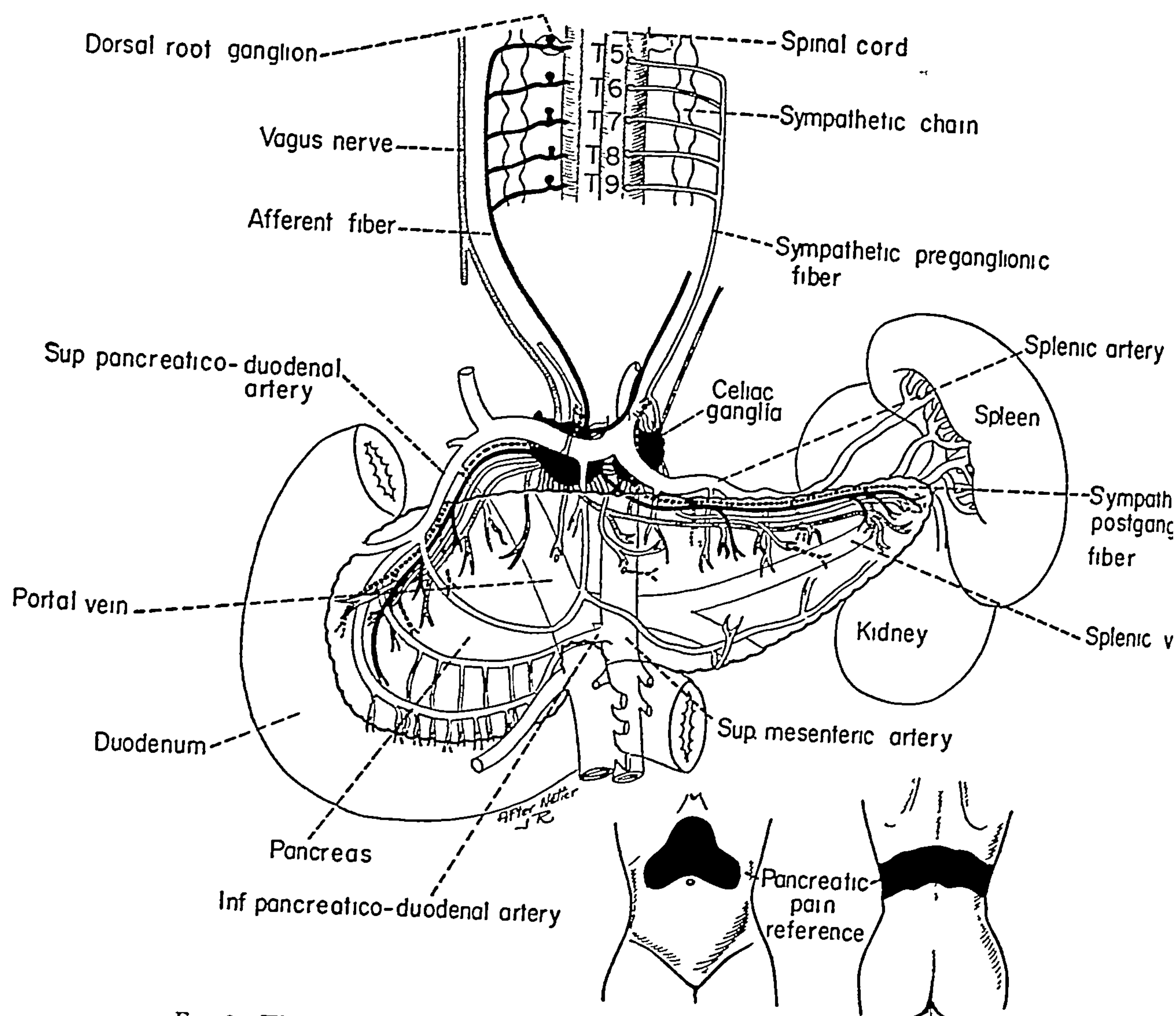


Fig 86 The pancreatic nerve supply is extensive and the blood supply diffuse

denal mucosa is inactive and contains not trypsin but its precursor trypsinogen The latter is activated by enterokinase, a constituent of intestinal juice (succus entericus) [42]

Regulation of Pancreatic Secretion

NERVOUS CONTROL The volume and the composition of the pancreatic secretion vary markedly under different conditions There is a small continuous secretion of pancreatic juice in the fasting animal and, although the mediation of this portion of the total secretion is unknown the hypophysis may have an influence (*see below*) Be this as it may food ingestion constitutes perhaps the most effective stimulus, and within a few minutes after the taking of food the flow of pancreatic juice is increased This response appears to depend on reflex stimulation of the vagi, for stimulation of the peripheral end of the cut vagus results i a flow of enzyme-rich juice This activity i accompanied by shrinkage of the gland cell and disappearance of intracellular granules Stimulation of the sympathetic supply t the pancreas results in a diminished volume of flow and a reduced enzyme content

THE HORMONAL REGULATION OF PANCREATIC SECRETION When fluid enters the duodenum—particularly acid, fat, or bile—the elaboration of a hormonal substance *secretin* is stimulated, and this substance is a powerful instigator of pancreatic secretion It is apparently liberated from the intestinal mucosa, and there is a qualitative difference in the pancreatic secretion produced by vagal stimulation as compared with that induced by secretin, the former being less in volume but richer in enzymes than the latter The relative importance in man of the vagal regulation of pancreatic secretion, as com-

pared with that of the hormonal stimulation by secretin, is not yet known

The most powerful effect from secretin is obtained when this material is given intravenously Given subcutaneously, it has a more prolonged but more variable action, it is ineffective by mouth In addition to secretin, there appears to be at least one other humoral agent (pancreozymin) that is liberated from the intestinal mucosa and which stimulates pancreatic flow this secretion being similar to that produced by vagal stimulation, the action of this hormone is not abolished by atropine, as is the vagal effect. However, both the pancreozymin and vagal effects can be imitated in man by the injection of a slowly acting acetylcholine-like substance such as mecholyl. Injection of mecholyl which acts at the vagal terminals has a slight effect on the volume of duodenal fluid, but produces a marked and prolonged increase in the output and concentration of all the pancreatic enzymes[42]

INFLUENCE OF DIET, DRUGS ALCOHOL, AND VAGOTOMY ON PANCREATIC SECRETION In animals meat elicits a large volume of pancreatic juice that is rich in alkali and poor in enzyme concentration Fat or milk produces a moderate volume of juice with a low alkali and high enzyme concentration, and bread produces an intermediate response[43] In man, McCaughan and his associates[20] found that the pancreatic flow was continuous but at a low level between meals, it was markedly increased for about 3 hours by taking food whether the food was rich in protein fat, or carbohydrate

In a patient studied by Howard and his associates[12] the administration of secretin in a dosage of 80 units intravenously produced a 350 per cent increase in hourly volume of pancreatic secretion. Moreover the secretory response initiated by the ingestion of food in their patient would appear to have constituted the chief basis for the greater volume of pancreatic secretion observed during the day as compared to the night Hildes Ferguson, and Bartlett[11] also noted that starvation caused a decrease in the rate of pancreatic secretion In an effort to localize anatomically the site where food or acid causes the release of secretin in the human being, Howard and his associates guided a Miller Abbott tube fluoroscopically into the upper jejunum The hourly volume of pancreatic secretion measured 3 ml A test meal consisting of 240 ml of acidified malted milk was then instilled by way of the tube into the jejunum. The resulting increment in pancreatic secretion was small, being 4 ml per hour as compared to the fasting level of 3 ml Next, the tube was withdrawn into the duodenum and the test meal again instilled. This resulted in a 400 per cent increase in pancreatic secretion The tube was then removed and an oral meal was found to increase the flow 900 per cent. A test meal of fat, protein, and carbohydrate given by Miller Abbott tube directly into the duodenum caused no change in pancreatic secretion but the same test meal when given through the tube into the stomach resulted in an increase of 125 per cent in the volume of secretion Atropine sulfate given intramuscularly decreased the hourly volume, but when this dosage and secretin were given simultaneously an increase in pancreatic secretion to 500 per cent was found. Similar results were obtained using banthine It was found that banthine would delay or prevent the secretory response to a test meal but that when banthine and secretin were given intravenously and simultaneously a typical secretin response occurred. They concluded that these studies indicated that neither atropine nor banthine could directly block the humoral response once the secretin had been released. Because of the high incidence of acute pancreatitis in alcoholics, the effect of alcohol on the secretin mechanism was also studied. Whisky (60 ml by mouth) was followed by a 50 per cent reduction in the volume of secretion 50 ml of ethyl alcohol given intravenously in glucose solution caused no change in secretion.

In a similar study of a patient with an

essentially complete external pancreatic fistula, Mahaffey and Haynes[18] found that approximately two-thirds of the pancreatic juice was secreted during the day and approximately one-third during the night Pancreatic secretion was continuous, but the volume of secretion varied from hour to hour and from day to day They made the point that to evaluate the response of pancreatic secretion to drugs by comparing a single one-hour volume of secretion as a control with a single one-hour volume of secretion following administration of a drug assumes a constancy of secretin formation which was not supported by their data Secretin, splanchnic block, and whisky each produced increases in the volume of pancreatic secretion, whereas banthine produced a moderate decrease during one test and an increase in another These findings were, of course, somewhat different from those reported by Howard *et al* [12]

Shingleton, Fawcett, and Vetter[39] found that the resting volume of duodenal secretion (reflecting pancreatic flow) was greater (5 1) in vagotomized than in normal subjects A vagal blocking agent (banthine) had an inhibitory effect on the response of the pancreas to the intravenous injection of secretin, again in contrast to the findings of Howard and his co-workers

From these several and at times conflicting reports, it is clear that additional study is required before the relative importance of neural, humoral, dietary, and other factors in the qualitative and quantitative aspects of pancreatic secretion can be defined

HYPOPHYSIAL REGULATION OF SECRETIN The concept that the gastrointestinal hormonal mechanisms are self-regulating entities, entirely independent of one another and of other hormonal structures, may require revision in view of the report of Dorcaster and Haist[5] regarding the effects of hypophysectomy on the secretin content of the rat intestine After developing a sensitive and reliable assay procedure, these workers determined the effect of body size and of hypophysectomy on the secreti tent of the rat gut In regard to the of body size, it was found that there no significant difference in the total am of secretin extractable from the inte of small and large rats, but that the co tration of secretin per gram of intestin minished significantly as the animal larger It was not determined whether decreased concentration was due to fa of growth of the structures elaborating cretin, or to a reduced concentratio secretin per unit of secretory struc Comparisons between normal animals animals subjected to hypophysectomy ceiving the same caloric intake) show significant reduction of extractable cretin in the animals that had under hypophysectomy in terms of total acti *activity per gram of dried intestine,* *activity per unit of body weight* Furt *more, the reduction in secretin was no* proportion to any difference in intesi weight However, since the secretin-secre cells of the intestine have not been identi it is not known whether the reduction in cretin following hypophysectomy is du atrophy of the secretin-producing structu or to a reduced production or decreased eration of secretin Finally, it has not b determined whether the atrophy of the p creas that occurs following hypophysecto is secondary to changes in secretin p duction

Effects of Total Pancreatectomy

The excision of the entire pancreas carcinoma, or for otherwise uncontrolla hypoglycemia due to hyperinsulinism, for chronic relapsing pancreatitis, has b performed in a number of instances and effects studied Although diabetes mellitu discussed elsewhere, it may be noted h that the diabetes which follows total pa createctomy is surprisingly mild in degr However, the absence of the external pa creatic secretion produces important dige tive disturbances, and large amounts of and organic nitrogenous substances are lo

in the stool The feces are bulky, light in color, soft occasionally loose or watery and sometimes foul smelling, the weight of the fecal solids is about 80 to 120 gm per day approximately 3 times the normal value On a daily fat intake of 100 gm, from 5 to 7 gm are normally lost in the feces, in contrast following total pancreatectomy one patient on a daily fat intake of 70 to 100 gm. lost 30 to 48 gm. in the feces[4] (Incidentally it has been demonstrated with isotopes that fecal fat does not necessarily represent only fat that has not been assimilated a portion of the fecal fat is 'secreted" into the bowel) The fat digestion that does continue in the absence of pancreatic lipase is due to the action of gastric and intestinal lipase Considerable fat is split even in the absence of pancreatic juice but this appears to be due largely to the lipolytic action of bacteria in the colon Little fat is absorbed in the large intestine.

The normal daily *fecal nitrogen* excretion is about 1 5 gm corresponding to about 10 gm. of protein though much of this represents the protein of the fecal bacteria Following pancreatectomy in one patient on a daily protein intake of 100 gm from 4 to 8 gm of nitrogen were lost daily, corresponding to from 25 to 50 gm. of protein Pancreatic proteolytic enzymes can then, be partially but not wholly replaced by gastric pepsin and intestinal erepsin.

Total pancreatectomy has little effect upon the digestion and absorption of carbohydrate indicating that pancreatic amylase can be wholly replaced by intestinal enzymes. (This phase of carbohydrate breakdown is of course not to be confused with the defective utilization of glucose which results from a lack of insulin) The imperfect digestion and absorption of fat and protein may lead to a loss of from 20 to 35 per cent of the ingested calories, but the administration of pancreatic digestive extracts by mouth may materially reduce the loss of foodstuffs in the feces Priestley and his associates[37] described a patient who survived total pancreatectomy for islet-cell adenoma and whose subsequent insulin requirement was from 20 to 30 units daily Her defective fat absorption was not improved by pancreatin, but a substantial decrease in fecal nitrogen followed its administration Whitfield and his associates[41] described the metabolic effects of total pancreatectomy in a man who survived total pancreatectomy for over two years In their subject the gross defect in fat absorption was greatly reduced by large doses of pancreatin, but the nitrogen balance was not improved by such therapy The insulin requirement in this patient was usually about 50 units per day or less

These and other reports indicate a considerable variability in the metabolic effects of total pancreatectomy in different patients

The rôle of the pancreatic enzymes in digestion and particularly in fat digestion, is still the subject of continued investigation For example while it has been held by many that bile is indispensable for fat absorption a considerable amount of fat can be absorbed in dogs with biliary fistulae Cohen and Annegers[4] found that in dogs lacking pancreatic juice only about 40 per cent of dietary horse meat nitrogen, 30 per cent of casein nitrogen, and little or no casein hydrolysate nitrogen were lost Nearly 40 per cent of dietary lard as well as oleic acid was lost in the feces of dogs lacking pancreatic juice However, the administration of sodium bicarbonate to partially depancreatectomized dogs (by means of indwelling duodenal cannulas) reduced the fecal loss of dietary oleic acid to that observed in normal dogs The bicarbonate in pancreatic juice seemed to account for the ability of normal dogs to absorb substantial amounts of fatty acid more completely than do dogs lacking pancreatic juice

With the conclusions of Annegers and coworkers in mind, Pessoa Kim and Ivy[35] studied fat absorption in the absence of bile and pancreatic juice in dogs The main objective of their study was to test the hydrolytic aqueous solution hypothesis of

fat absorption by comparing the absorption of neutral fat and its constituent free fatty acids in normal, biliary-fistula, and pancreatic-duct-ligated dogs. They found that normal dogs absorbed triglycerides and fatty acids better than dogs deprived of bile or pancreatic juice. However, a considerable amount (70 per cent) of neutral fat, as corn oil, and of fatty acid (55 to 75 per cent) as corn-oil-fatty-acids and oleic acid, was absorbed in the absence of bile or pancreatic juice; this showed that neither bile nor pancreatic juice was indispensable for the absorption of any of the fats and fatty acids studied.

Use of Labeled Fat and Fatty Acid in the Study of Pancreatic Disease

Labeled fat is being used successfully in the study of pancreatic disease.[33] Reasoning that the over-all process of intestinal fat absorption could be divided arbitrarily into two phases, *enzymatic digestion* and *absorption*, Reemtsma, Malm, and Barker[28] utilized I^{131}-labeled neutral fat (olive oil) and fatty acid (oleic acid) to separate these two phases of fat assimilation. Patients with "pure" pancreatic deficiency (surgical removal of the pancreas, obstruction of the pancreatic duct, or fibrous replacement of the pancreas) showed marked impairment of fat absorption but normal fatty acid absorption; that is, pancreatic enzymes were not available to split neutral fat to fatty acids, but when fatty acids themselves were fed absorption proceeded normally. In contrast, patients with malabsorption due to causes other than pancreatic deficiency demonstrated marked impairment of both neutral fat and fatty acid absorption.

Pancreatic Function Tests

The pancreatic function tests are not so specific as the clinician might wish them to be. Some of them will be reviewed.

SERUM AMYLASE LEVEL. In 1929 Elman and his associates[9] demonstrated the diagnostic importance of an elevated serum amylase level in acute pancreatitis, and since that time this has come to be relied upon as the principal laboratory evidence of acute pancreatitis. The normal serum amylase level in our hospital ranges from 70 to 300 Somogyi units per 100 ml. of plasma. In acute pancreatitis this level may rise to 1000 units or even to 1500 units. It usually increases rapidly during the first 48 hours, persists for a variable number of days, and then gradually falls to normal. When the serum amylase level is markedly elevated and other clinical findings are compatible with pancreatitis, the diagnosis of pancreatitis is highly likely. Nevertheless, it is now appreciated that the serum amylase level may be—and commonly is—increased in the presence of a ruptured peptic ulcer. The administration of morphine sulfate may, by causing spasm of the sphincter of Oddi, produce a rise in the serum amylase level, as will abdominal trauma. Indeed, almost any acute condition within the abdomen may be associated with a rise in the serum amylase level, though the rise in conditions other than pancreatitis is rarely of the degree seen in this disease.

In contrast to acute obstruction, in chronic conditions which result in the obstruction of the pancreatic duct, such as tumors, cysts, and chronic pancreatitis, the serum amylase level may be normal. Here the presence or absence of a rise in the pancreatic amylase level in response to secretin injection may be more helpful. Sanchez-Ubeda and Rousselot[34] reported that the serum amylase level was significantly elevated in only 1 of 31 "normal" patients given secretin and methacholine (mecholyl), whereas 5 of 7 patients with chronic pancreatic disease showed a significant elevation. On the other hand, Shingleton and his associates[18] did not find the serum amylase of diagnostic value after stimulation by secretin alone, or after urecholine and secretin, in patients with chronic pancreatic disease.

SERUM LIPASE. The serum lipase level is also increased in pancreatitis. It becomes elevated early in the attack and remains at a high level for several days longer than do

the amylase level Although some consider the serum lipase level more useful than the amylase level in the diagnosis of pancreatitis, the former is more tedious to measure and thus is of less value clinically in deciding whether or not the individual has the disease The serum amylase level can be determined within an hour or so

URINARY DIASTASE. Diastase (starch splitting enzyme) is absorbed from the alimentary tract into the blood stream and is excreted by the kidneys In acute pancreatitis the urinary diastase level is usually increased.

DUODENAL DRAINAGE AND ANALYSIS OF PANCREATIC SECRETION The use of an indlying duodenal tube for aspiration of the pancreatic secretion has been widely employed since the work of Lagerlof[10] was published in 1942 Using secretin as a stimulus, samples of duodenal juice were obtained through the tube The control analyses included measurement of the volume of secretion bicarbonate content and the pancreatic enzymes amylase trypsin and lipase

Even though values obtained by duodenal aspiration vary widely in normal individuals, significantly low values are often observed in patients with proved pancreatic disease Accordingly the absence of these enzymes in the duodenal secretion is indicative of decreased pancreatic function and occurs in such diseases as chronic pancreatitis.

It has been stated that cytologic studies of aspirated duodenal contents may help in the diagnosis of carcinoma of the pancreas but we have had no experience with this technic

Shingleton and his associates[38] studied the duodenal secretion in 75 patients employing secretin as a stimulus (1 unit per kg. Lilly) Twenty six of these tests were in patients with suspected pancreatic disease but the results were excluded because the diagnoses were not definitely proved Additional tests were done in 18 patients without disease 9 with chronic relapsing pancreatitis 4 with carcinoma of the pancreas 7 patients who had undergone transthoracic sympathectomy with splanchnicectomy for hypertension and 6 patients who were under the influence of a vagal blocking drug Vagotomized and sympathectomized patients were tested 3 to 5 years postoperatively and the diagnosis in all patients suspected of having chronic pancreatitis and pancreatic carcinoma was proved by operation A special 4 lumen tube was positioned under fluoroscopic control in the duodenum, and a 30 minute sample of duodenal juice was obtained before and after the intravenous injection of secretin A significant reduction in volume, amylase concentration, and total amylase output were found after secretin injection in the patients with chronic pancreatitis and pancreatic carcinoma, and in vagotomized patients and those under the influence of the vagal blocking drug

Although the duodenal suction method of study is admittedly time-consuming, uncomfortable to the patient, and may fail to show early derangement in pancreatic function, it is a useful tool in the further development of our knowledge of pancreatic physiology

PANCREATIC FUNCTION AND BLOOD CLOTTING That a relationship exists between pancreatic function and blood clotting has been long suspected, and the literature regarding this subject was reviewed by Storer and Kazdan [40] They noted that multiple venous thrombi may be more frequently associated with carcinoma of the body or tail of the pancreas than with other types of carcinoma and, further, that a hemorrhagic tendency (consisting of both bleeding and perhaps an increased red cell fragility) is a characteristic finding in acute pancreatitis They correlated the prothrombin time with the serum amylase and serum trypsin levels in cases of acute pancreatitis, and concluded that alterations in the serum trypsin levels might be responsible for the increased clotting tendency associated with carcinoma of the pancreas and for the bleeding tendency observed in acute pancreatitis It is known that the immediate effect of the intr

injection of trypsin is a temporary decrease in plasma antithrombin, therefore, an increased production of trypsin such as is seen in acute pancreatitis might lead to venous thrombosis Moreover, the secondary sustained elevation of the antithrombin factor, which occurs after an increase in trypsin levels, could conceivably lead to peripheral hemorrhagic tendencies

Shingleton, Anlyan, and Hart[38] found by using a sensitized clotting test before and after the administration of pancreatic stimulant that a change in blood coagulability could be demonstrated in a significant number of patients with chronic relapsing pancreatitis and pancreatic carcinoma These authors considered that in chronic pancreatic disease there exists some obstruction to the free flow of pancreatic enzymes during stimulation and that trypsin, entering the circulating blood, is responsible for the observed changes in coagulability It appeared also that the removal of the pancreatic external secretion prolonged the blood clotting time On the basis of their studies, plus reports from the literature, Shingleton and his associates suggested the following tentative hypothesis regarding the effects of trypsin and trypsin antagonists on blood coagulation small amounts of trypsin will promote the coagulation of blood by the conversion of prothrombin to thrombin, whereas larger amounts produce shock with prolongation of clotting time due to the consumption of prothrombin and fibrinogen secondary to massive intravascular clotting

Acute Pancreatitis

In the past, acute pancreatitis has usually been classified into two types, the *acute edematous* and *acute hemorrhagic* (necrotizing) forms Yet, more and more it seems likely that the two may represent varying degrees of the same process Of course, edema from surrounding inflammation, such as that associated with ruptured peptic ulcer, may also involve the pancreas

Etiology of Acute Pancreatitis

(1) The "common channel" theory has long had many adherents, and it has about it an appealing simplicity In essence, this hypothesis holds that fusion of the bile and pancreatic ducts into a common channel at the ampulla of Vater allows bile to activate pancreatic digestive enzymes, which then destroy pancreatic tissue As early as 1901 Opie[24] proposed that a gallstone impacted at the sphincter of Oddi was essential in the pathogenesis of acute pancreatitis, but, since studies failed to confirm this finding in a significant percentage of cases, spasm of the sphincter was later proposed as an alternative factor in the production of "common channel" pancreatitis (Fig 87) Obstruction

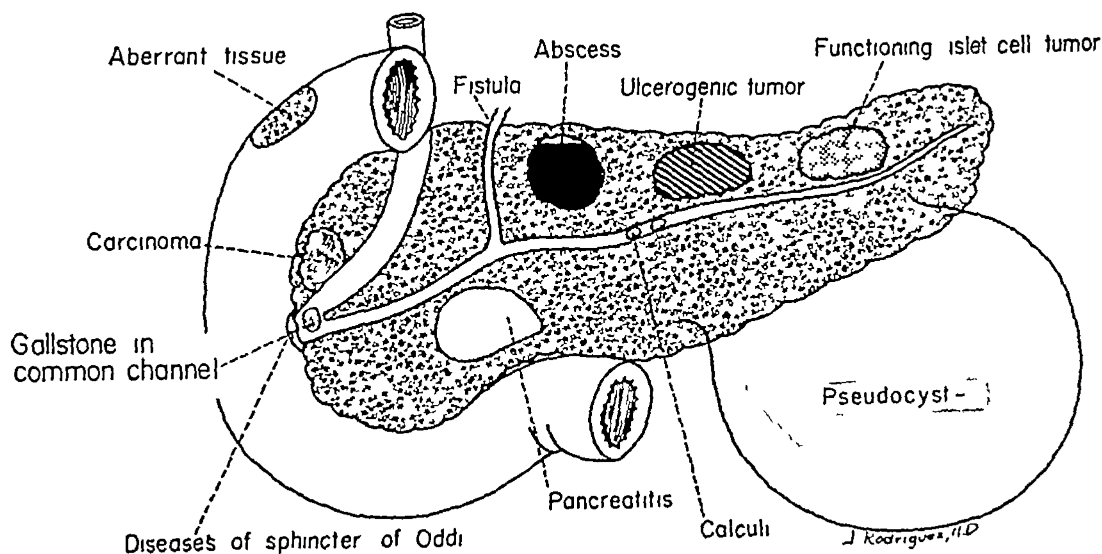


Fig 87 Diseases of the pancreas Pancreatic exocrine hypofunction leads to meconium ileus in infants and sprue in adults Endocrine insufficiency results in diabetes mellitus

of the main or lesser pancreatic ducts—whether by calculus, inflammation, or epithelial metaplasia—also has been advocated as an important factor. Pancreatitis may be produced in dogs by injecting bile into the pancreatic duct under pressure.

Regardless of the conflict between different theories, *there is evolving a perhaps general belief that the important initial defect in the genesis of pancreatitis is that the organ is attacked by the ever present trypsin—"whether because its inhibitor has been destroyed in the presence of an altered blood supply or because the old enzyme has a new unusual activity, or because a new enzyme is present with an additional effect."*[13]

That a common channel does exist in a considerable number of patients has been verified by numerous studies. First, in approximately 65 per cent of normal individuals it can be shown by anatomic studies at autopsy that the main pancreatic duct and the common bile duct enter a common channel before being discharged into the duodenum at the ampulla of Vater. Second, cholangiography performed through a T tube frequently shows a reflux of the injected radiopaque medium from the common duct into the main pancreatic duct in normal individuals and in an even greater proportion of individuals with pancreatitis. In patients having a common channel demonstrated by cholangiography, various workers have found that many will exhibit a distinct rise in blood amylase following reflux of the dye into the pancreatic duct. Third, Popper[38] demonstrated pancreatic enzymes in gallbladder bile in 20 of 200 people without pancreatitis and in 16 of 18 people with the disease.

For the sake of objectivity, however, one should cite some of the evidence that casts doubt upon the validity of the common channel factor as being the only or even the major cause of acute pancreatitis. First, the reflux of bile into the main pancreatic duct is demonstrated in many patients who show no clinical evidence of pancreatitis, and of the 65 per cent of normal individuals who can be shown at autopsy to have a common channel, relatively few have had evidence of pancreatitis during life. Second, the pressure necessary to produce pancreatitis experimentally, by the injection of bile into the pancreatic ducts, is greater than can be physiologically developed by the gallbladder and liver.

As for obstruction of the ampulla by a calculus, Schmeiden and Sebening[36] found only 57 cases of ampullary stones in 1278 cases of pancreatitis. Rousselot[32] emphasized that whereas spasm of the sphincter of Oddi is postulated as a cause of obstruction, such spasm has not been demonstrated experimentally. It is generally agreed that rupture of the pancreatic radicles is necessary if pancreatitis is to be produced by injection of bile into the pancreatic duct, yet, it is difficult to conceive of a pressure gradient sufficient to rupture the acini that could be generated under clinical conditions in a common biliary pancreatic system. Fine[37] found that the injection of bile at a pressure of 460 to 600 mm. Hg ruptured the pancreatic ductules and produced hemorrhagic pancreatitis, but under clinical circumstances spasm of the sphincter of Oddi would probably give way before such pressure was achieved. Doubilet and Mulholland[8] found the normal sphincteric resistance to be about 150 mm. H_2O, which rose to about 300 mm. after spasm induced by morphine. Finally, further attacks of pancreatitis may occur when the common bile duct has been anastomosed to a defunctionalized Roux Y loop where there is no possibility for an admixture of bile and pancreatic juice in the pancreas.

It is apparent, therefore, that while the "common channel" theory is an extremely attractive hypothesis, it does not fit all circumstances.

SOME FURTHER FACTORS WHICH MOST PATIENTS WITH PANCREATITIS HAVE IN COMMON. Over 50 per cent of patients with pancreatitis have *gallstones*, and cholelithiasis has been found to be 6 times more common in autopsies on patients with pancreatitis than

in a control group of autopsies on patients without pancreatic disease [1] Nevertheless, the majority of patients with cholelithiasis do not have pancreatitis, and cholecystectomy and common duct drainage for pancreatitis do not always prevent further attacks of the disease On the other side of this argument, however, is the fact that removal of the gallbladder and adequate exploration and drainage of the common duct frequently do end the attacks of pancreatitis

An additional factor is that of *alcoholism* A very considerable percentage of patients with pancreatitis are chronic drinkers Here again, though, the way in which alcohol enhances the probabilities of pancreatitis remains to be explained It is known that alcohol in small amounts may stimulate both hydrochloric acid and pancreatic secretion Richman and Colp[29] found that alcohol *per se* in contact with the duodenal mucosa produced large amounts of secretin In higher concentrations this agent is inhibitory to both hydrochloric acid and pancreatic secretions It causes marked irritation of the gastric and duodenal mucosa, and some have suggested that duodenitis is produced by alcohol and may cause occlusion of the ampulla, resulting in pancreatitis when a common channel is present

Increased vagal tonus may also be important in the etiology of pancreatitis As has been seen, overactivity of the vagus nerves results in an enzyme-rich secretion A second way in which the increased vagal tone may influence pancreatic function is by increasing the gastric secretion of hydrochloric acid, this acts on the duodenal mucosa to stimulate the elaboration of secretin, the main stimulator of pancreatic flow Ripstein and Thompson[31] reported a study in dogs in which the mortality in experimental pancreatitis was reduced from 75 per cent in one group to 24 per cent in a second group protected by vagotomy Similar results were obtained by Schaffarzick and his associates [35]

Finally, still other causes of pancreatitis include trauma, systemic disease, bacterial infection, penetrating duodenal ulcer, and vascular accidents

The Clinical Attack of Pancreatitis[44]

Acute pancreatitis usually occurs in middle-aged patients and most typically in the obese and overindulgent male It occurs also at times in young and otherwise healthy adults There is frequently a history of gallbladder disease and perhaps of previous acute attacks of pain similar to the current one Often the episode follows a heavy meal or alcoholic intake The radiation of the pain has been described In brief, the onset is acute and the distress is most marked in the epigastric region, perhaps extending to either the right or the left subcostal region or to the left subscapular, left lumbar, or left shoulder region The pain is more or less constant and boring in nature, and is usually severe

In severe cases of hemorrhagic or necrotizing pancreatitis, the patient exhibits a rapid pulse, cold clammy skin, cyanosis, and hypotension This shock is initially due largely to intra-abdominal blood and fluid extravasation with resulting oligemia, this is reversible, but eventually the more obscure irreversible shock may develop The fundamental cause of the irreversible shock of necrotizing pancreatitis is disputed Some observers favor bacterial effects, and others favor products of tissue digestion In any event, vomiting is often severe and persistent, associated with upper abdominal tenderness and rigidity which may become diffuse as the pancreatic enzymes spread

While these are among the clinical findings in the more severe cases of pancreatitis, the findings in acute edematous pancreatitis may consist of little more than moderate pain and the patient is not critically ill In fact, unless the serum amylase level is requested in all patients with upper abdominal pain, many mild cases of pancreatitis will be missed

While a sharply elevated serum amylase level is the aid which establishes the diag-

nosis in most cases, this level may decline to below diagnostic levels within 48 to 72 hours after the onset of the disease To extend the period of the time during which amylase de terminations may be of diagnostic value Keith, Zollinger, and McCleery[14] studied the amylase level in fluid obtained by para centesis In pancreatitis this fluid contains pancreatic enzymes in a high concentration and Keith and his associates found that with the patient in the sitting position suffi cient peritoneal fluid could be obtained by careful paracentesis to perform the amylase test As little as 0.2 ml could be diluted 10 times and a satisfactory determination ob tained by the Somogyi method Inasmuch as the peritoneal fluid amylase level may remain elevated for from 2 to 3 days following a return to normal levels of the serum amyl ase concentration, this test extended in their hands the length of time in which amylase determinations were of diagnostic aid in pancreatitis An incidental additional find ing was the fact that by analyzing the peri toneal fluid for bile and by titrating for total acidity, in addition to determination of the amylase value the peritoneal tap could be of differential diagnostic aid in identifying cases of perforated peptic ulcer

The *total serum bilirubin* level is usually elevated, as is the *leukocyte count*

The *serum calcium level* may be sharply depressed due to the incorporation of large amounts of calcium with the so called fat necrosis, which actually represents the for mation of calcium soaps In fact the amount of calcium that may be recovered from the pancreas in fatal cases can be far more than can be accounted for on the basis of losses from the extracellular fluid Moyer[22] has called attention to a possible etiologic relationship between calcium metabolism and pancreatitis, and we encountered acute pan creatitis in an elderly man who died of pneumonitis-emphysema pulmonary insuffi ciency approximately nine days following removal of a huge parathyroid adenoma (p 562)

Roentgen examination may exhibit the

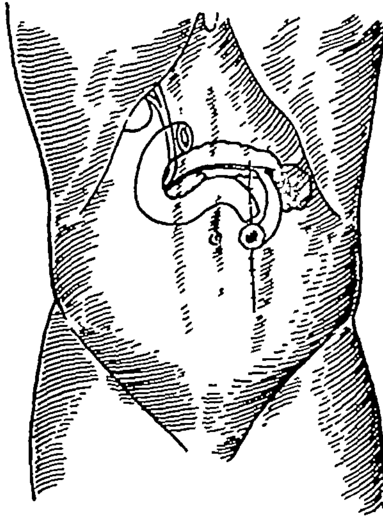




Fig 88 Necrotizing pancreatitis *Above* Widespread fat necrosis Note incidental leiomyoma of small bowel *Below* Necrosis of entire pancreas and surrounding tissue

bowel patterns of paralytic ileus, widening of the duodenal loop on the barium study, gallstones and possibly pancreatic calcification if the acute attack is but a recru descence of chronic pancreatitis.

The gross *pathologic finding* is an enlarged and usually soft and friable organ There is marked edema and often much hemorrhage and necrosis of pancreatic tissue depending upon the severity of the disease (Fig. 88) The findings may be confined to one portion of the pancreas, such as the head or tail, or may involve the entire organ Most characteristic and helpful in the mor phologic diagnosis are yellowish white spots in the surrounding fat, representing 'fat necrosis' (Fig. 88) As noted above this does not actually constitute fat necrosis but is the result of the chemical change produced by pancreatic lipase which splits neutral fat into glycerol and fatty acids. The fatty acids combine with ionizable calcium to



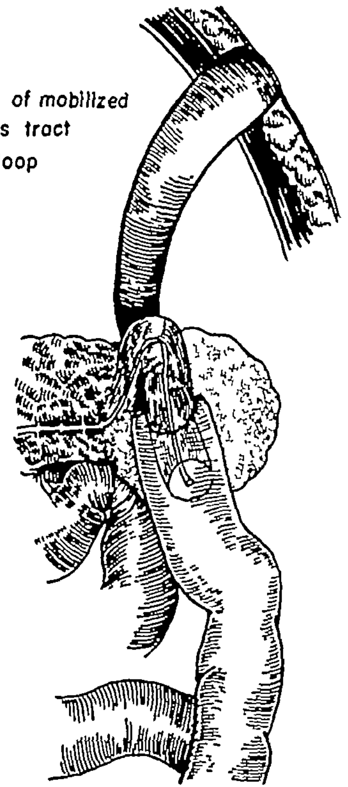


Fig 91 Left This patient had developed a chronic pancreatic fistula Note abscess at tail of organ *Right* Fistulous tract implanted in isolated Roux-Y loop of jejunum when abscess rendered excision impracticable (From HARDY, J D, AND BOWLIN, J W Some complications of pancreatic disease Illustrative cases with notes on management Ann Surg, **145**: 848, 1957)

tous compression of the intrapancreatic portion of the common bile duct, but if it is due to a common duct stone or fibrous stricture of the sphincter operative correction will be in order *Diabetes mellitus* of varying degrees of severity may be observed from time to time Lastly, one of the most sinister complications of acute pancreatitis is the development of *chronic relapsing pancreatitis*

Chronic Relapsing Pancreatitis

There are those who consider chronic relapsing pancreatitis a disease in itself, but most observers believe that chronic pancreatitis results from repeated attacks of acute pancreatitis, gradually progressing in severity Treatment is distressingly unsatisfactory Rousselot[32] reviewed the various treatments for chronic relapsing pancreatitis and concluded that the lack of consistency of results was due in considerable measure to the lack of care with which the diagnosis of chronic pancreatitis had been established He advocated the following rigid criteria for the diagnosis of this condition First, there must have been repeated bouts of abdominal pain, accompanied by a significant elevation of amylase and lipase content of serum or urine or both (He emphasized that one episode of pancreatitis does not signify that chronic relapsing pancreatitis is present, and more than one such attack must occur before this condition can be said to exist It is well known that a considerable number of initial attacks of acute pancreatitis are followed by no sequelae, or at least are followed by prolonged asymptomatic periods This is particularly likely when the pancreatitis accompanies cholecystitis with cholelithiasis and adequate gallbladder surgery is carried out) Second, there should be biopsy evidence at operation of fat necrosis, edema of the gland, cyst formation, and acute or chronic inflammation Third, symptoms accompanied by one or more of the following manifestations must point to the diagnosis of chronic atrophic pancreatitis, even in the absence of elevated serum enzymes alteration in carbohydrate metabolism or in fat

digestion, demonstration of pancreatic calcification by x ray, and repeated—and significantly low—pancreatic secretion as demonstrated by duodenal drainage Rousselot emphasized that it is unlikely that massive pancreatic damage or repeated injury to the pancreas of any degree will not leave some residual anatomic stigmata that can and should be diagnosed by biopsy and microscopic examination of the tissue Failure to do this will result in reports from various clinics that cannot be compared

Physiologic Considerations in the Management of Chronic Relapsing Pancreatitis

Since no uniformly successful method of treatment currently exists for the management of chronic relapsing pancreatitis it was to be expected that many different types of management would be proposed A number of these will be presented briefly along with the physiologic rationale advanced to support the procedure

CHOLECYSTECTOMY AND CHOLEDOCHOSTOMY FOR REMOVAL OF GALLBLADDER AND COMMON DUCT STONES, WITH PROLONGED DRAINAGE OF THE COMMON BILE DUCT This operation has much to recommend it since gallstones are associated with pancreatitis in a large proportion of cases Moreover symptoms commonly disappear permanently when adequate gallbladder and common duct surgery has been performed The precise relationship which exists between gallstones and pancreatitis has never been explained for the circumstance of gallstones blocking the ampulla of Vater with resulting reflux of bile into the pancreatic ducts is a relatively rare finding. However definitive gallbladder and common duct surgery should be performed as soon as the acute attack of pancreatitis has become quiescent

SPHINCTEROTOMY This operation has been sponsored enthusiastically by Doubilet and Mulholland[6, 7] The rationale upon which it is based is that increased resistance at the sphincter of Oddi results in a reflux of bile into the pancreatic ducts The sphincter is divided at one point either by the use of a sphincterotome passed down the common duct or under direct vision through a duodenal incision Not all authors are agreed as to the value of the operation, but an increasing number of surgeons are performing it There remains no question in our mind that stenosis of the sphincter does occasionally occur In one woman who had had repeated attacks of pancreatitis associated with mild jaundice the common bile duct was explored and when no catheter or Bakes dilator could be passed through the sphincter into the duodenum, the duodenum was opened and the papilla inspected The papilla and the immediate surrounding tissues were quite hard and fibrous, and renewed flushing of the common duct with saline under pressure revealed a pin point opening in the papilla, with only a small trickle of saline emerging The papilla and the sphincter were incised radially at one point on the circumference (Fig 92) During an 18-month follow up she had had no recurrence of abdominal pain or jaundice Yet the possibility of further fibrosis in a divided sphincter is perhaps a real one Moreover, the cholecystectomy that was performed in our patient may also have been beneficial Regardless of any other considerations, though this individual did have a fibrous stenosis of the sphincter of Oddi

VAGOTOMY McCleery Kesterson, and Schaffarzick[21] treated recurrent acute pancreatitis by vagotomy on the basis that neurogenic stimuli had an important rôle in the etiology of recurrent pancreatitis Vagotomy was performed in 11 patients and resulted in definite improvement in all It will be recalled that Ripstein[31] was able to reduce the mortality in acute experimental pancreatitis in dogs by prior vagotomy Nevertheless this operation has not enjoyed wide use in the management of chronic relapsing pancreatitis

GASTRIC RESECTION The rationale of this procedure in the control of chronic relapsing pancreatitis is that the food and gastric acid are diverted from the duodenum and thus

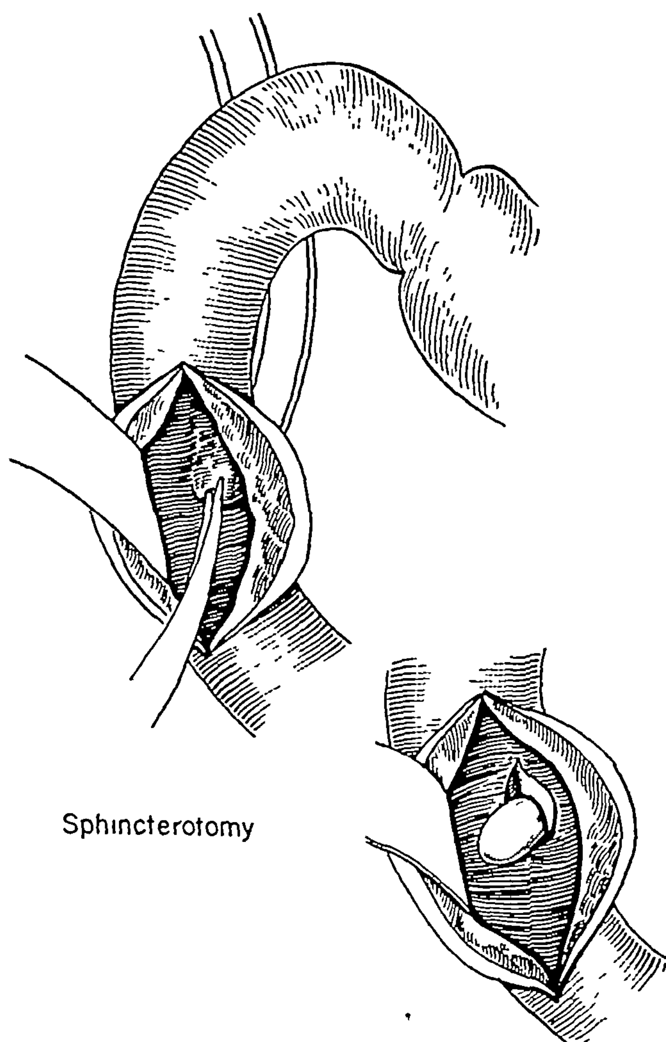


Fig 92 This patient had a definite fibrous stricture of the sphincter of Oddi, a rare finding in our experience (From HARDY, J D, AND BOWLIN, J W Some complications of pancreatic disease Illustrative cases with notes on management Ann Surg, **145**. 848, 1957)

secretin formation should be diminished Relatively few cases have been treated in this manner The *combination of gastric resection and vagotomy* has also been employed in a few cases

CHOLEDOCHOJEJUNOSTOMY This procedure was proposed by Bowers and Greenfield [3] The operative technic consists of boldly dividing the common bile duct, ligating the distal end, and anastomosing the proximal end to a Roux-Y loop of jejunum At the time of their report five patients had been operated upon and had responded favorably However, the follow-up period had been too short to permit definitive conclusions regarding this means of therapy in a disease in which remissions are common and most therapeutic measures unreliable

SYMPATHECTOMY In 1947, Reinhoff and Baker[30] performed transthoracic sympathectomy and vagectomy as a means of treatment for chronic relapsing pancreatitis They felt that the treatment was successful in their patients, and suggested that it be given additional trial Actually, Mallet-Guy and de Beaujeu[19] had treated chronic pancreatitis by unilateral splanchnicectomy several years earlier

While the pain can be, and frequently is, relieved by nerve section, the progressive nature of the disease is not halted by this treatment, and dietary disturbances, abscess formation, pseudocysts, jaundice and other complications are likely to continue

PANCREATIC RESECTION In a few instances resection of all or a part of the pancreas has been resorted to for the relief of jaundice, pain, or both Yet this is a formidable undertaking at best and is not to be lightly entered into If no jaundice is present and only pancreatic stones with associated pain need be managed, splanchnicectomy may be adequate

Summarizing Comment

At the present time there is no generally effective means of management for chronic relapsing pancreatitis Far too many of these pitiable individuals become opiate addicts as the months and years of distress pass by Needless to say, the possibility of coexistent pancreatitis and carcinoma should be excluded by liberal pancreatic biopsy, for if cancer is found no further effort need be made to avoid adequate opiate dosage Cancer is often overlooked initially

Fibrocystic Disease of the Pancreas

Fibrocystic disease of the pancreas is a disease of infants and children and is characterized by widespread fibrocystic changes not only in the pancreas but in other organs such as the lungs, liver, and kidneys There is virtually complete loss of external (exocrine) pancreatic secretion due to malformation of the ducts, a deficiency which gives rise to the disease known as meconium ileus

In this condition the intestine is obstructed by masses of inspissated meconium, usually in the distal ileum, and removal of the sticky meconium presents a difficult problem Olim[23] found that a dilute solution of hydrogen peroxide facilitated cleansing at operation by effecting separation of the meconium from the bowel wall This technic has not had a wide trial as yet Gross[10] has performed a double-barreled ileostomy, irrigating the distal loop postoperatively Later the bowel continuity is restored Koop[15] also has used ileostomy for this purpose

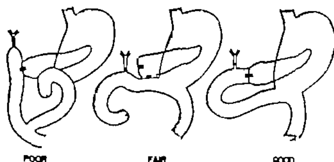


Fig 93 Methods of reconstruction following pancreatoduodenectomy The incidence of complications following pancreatoduodenectomy is considerable and those associated with the management of the pancreatic duct are the most formidable (Modified from RHOADS J E In *Surgery—Principles and Practice* edited by Allen J G Harkin H N, Moyer C A and Rhoads J E, Philadelphia, J B Lippincott 1957)

Tumors of the Pancreas

Islet-Cell Tumors

INSULIN SECRETING (BETA-CELL) TUMORS Hyperinsulinism is discussed under 'Surgical Endocrinology' (p 586)

"ULCEROGENIC" TUMORS Zollinger and Ellison[43] have emphasized the role which certain tumors of the delta (?) cells of the islets of Langerhans may have in the pathogenesis of an extremely vicious type of peptic ulceration, associated with markedly elevated levels of acid and total volume of gastric secretion Unless the tumor is found and removed, the surgical procedures usually employed for the management of the ulcer diathesis are likely to be followed by prompt ulcer recurrence The mechanism by which these tumors cause peptic ulceration is obscure, since no humoral secretion by them has been identified Occasionally they may be associated with hyperinsulinism but this is not usually the case The tumors are frequently malignant A patient with "malignant" acid secretion was reported by Machella Rhoads and Hobler in 1949[17] This man may have represented a case of ulcerogenic tumor of the pancreas though such tumors had not been described at that time

Pancreatic Carcinoma

Pancreaticoduodenal resection for carcinoma of the head of the pancreas or of the ampulla is hazardous mainly because complications are severe In Figure 93 it may be seen that anastomoses involve the common bile duct, the jejunum and stomach and the pancreatic duct. The most common and the most serious of these complications is pancreatic fistula and this often ends fatally The number of patients living and free of metastases at the end of five years is probably less than 5 per cent

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Chapter 13

Blood Transfusion Problems, Bloodclotting and Coagulation Defects, and Splenic Dysfunction

Blood Transfusion Problems[23]

Blood Groups: A Few Fundamentals

THE ABO SYSTEM The importance of blood groups in blood transfusion is so well known that they need only be mentioned here In 1901 Landsteiner[11] demonstrated that human beings could be divided into four groups depending upon whether the red cells contained one (A) or another (B) agglutinogen, or both (AB), or neither (O) With this knowledge transfusion was made relatively safe, but reactions were still frequent

THE MN GROUPS Landsteiner and Levine[12] demonstrated the entirely different M, N, and MN groupings While these did not often cause hemolytic reactions, it was concluded that upon occasion, and particularly after repeated transfusions, they could do so

THE Rh SYSTEM In 1940 Landsteiner and Wiener[13] discovered the Rh system, using sera prepared by the sensitization of various animals to the red cells of the Rhesus monkey They found that the red cells of about 85 per cent of white persons were agglutinated by anti-Rhesus (anti-Rh) serum, the other 15 per cent failed to react in this way The reactors were termed Rh positive and the nonreactors Rh negative Since the original description of these groupings, the Rh problem has been made far more complex through the identification of subgroupings of Rh antigens Nevertheless, in general the practical importance of the Rh factors lies essentially in avoiding the administration of Rh positive blood to an Rh negative recipient The first such transfusion does not usually result in a reaction, but it serves as an antigen to begin sensitization of the recipient to subsequent transfusions of Rh positive blood Further, it is particularly important to avoid transfusing fertile Rh negative women with Rh positive blood Levine, Katzin, and Burnham[14] first demonstrated an abnormal hemagglutinin in the serum of mothers of infants with erythroblastosis fetalis, an hemagglutinin which agglutinated the red cells of the infants as well as of the fathers It was subsequently shown that erythroblastosis fetalis is the result of immunization of the mother to the Rh positive cells of the fetus, thereafter, the Rh agglutinin so produced in the mother passes into the circulation of the infant and destroys its red cells A severe hemolytic anemia develops and is manifested by jaundice, anemia, and pigment deposition The disease usually does not manifest itself until the end of a second or third pregnancy, just as the first transfusion of Rh positive blood to an Rh negative recipient does not produce a reaction However, it is believed that an Rh positive transfusion can sensitize an Rh negative girl for life, thus predisposing to trouble even with her first pregnancy

Other blood groupings are known and

these are especially useful in medicolegal problems For example it is estimated that in paternity suits a falsely accused man can be exonerated in more than 50 per cent of cases if the ABO MN, and Rh tests are all known for child mother, and accused man With certain other known groupings this figure can be increased to 60 per cent [23]

Complications of Blood Transfusion

Considering the enormous amount of blood transfused each year in most large hospitals it is perhaps surprising that serious or fatal reactions do not occur more frequently That such does not occur is a tribute to the elaborate safeguards that blood banks have established And yet usually due to carelessness there still occur enough serious reactions to dispel any tendency to complacency These reactions range from mild febrile episodes to the hemolytic phenomena that lead to renal shutdown (Fig. 94)

The greater the care with which cross matching is carried out the fewer serious reactions there will be The red cells of the donor should be mixed with the serum of the recipient and those of the recipient with the serum of the donor If no agglutination of the cells of either is seen under the low power of the microscope, the blood is usually safe for transfusion—though this may not be so after repeated transfusions, pregnancies, or in patients with blood dyscrasias

1 FEVER WITH OR WITHOUT CHILLS The commonest reaction to transfusion consists of varying degrees of fever The more marked elevations are likely to follow a chill The cause of such reactions is not always apparent though it has been shown that careful cleansing of equipment reduces the incidence of these phenomena The more serious ones are those which follow the infusion of contaminated blood—a special danger if blood has been allowed to remain out of the refrigerator for more than a short while before transfusion The transfusion of blood heavily contaminated with bacteria can result in a chill and high fever that are followed by shock and death

Additional causes of minor reactions are listed in Figure 94

TRANSFUSION REACTIONS

Type	Cause	Frequency
		Per Cent
Pyrogenic	Bacterial pyrogens etc	1 8–2 0
Urticarial	Sensitivity to (?)	0 8–1 1
Hemolytic	Mismatched blood	0 1–0 5
Isosensitization	Sensitization through repeated transfusions and in pregnancy	Not rare
Circulatory overload	Injudicious augmentation of blood volume	Not rare
'Cold reaction	Cold agglutinins (?)	Not rare
Transmission of disease	Homologous serum jaundice Syphilis malaria, etc	0 45–1 0—rare
Plasma sensitivity	Heat labile plasma factor	Especially in paroxysmal nocturnal hemoglobinuria (PNH)
Infections	Grossly contaminated blood	Rare
Air embolism	Entry of air into veins	Rare
Fat embolism	Transfusion via bone marrow	Rare
Hypocalcemia	Exchange transfusions	Not rare
Hemorrhagic diathesis	Massive transfusions etc	Rare (?)

Fig 94 Many minor transfusion reactions are never satisfactorily explained but these become less frequent as knowledge of blood factors continues to unfold (From WINTROBE, M M *Clinical Hematology* Ed 4 Philadelphia Lea & Febiger 1956)

MASSIVE TRANSFUSION AND OVERTRANSFUSION. It is remarkable how much well-matched blood can be transfused, when required, without detectable ill effect It is not at all unusual to use upwards of 15 pints during resuscitation of a patient or during operation for aneurysm; and if significant shock is prevented such patients do well—despite the fact that the total circulating blood volume may have been replaced several times. This is not to say of course, that untoward effects do not occur in some patients following massive transfusion. When complications do arise following massive transfusions of well-matched blood they are apt to represent *coagulation defects* and *overtransfusion.*

Overtransfusion can readily occur in children, and it can readily occur in adults following pneumonectomy or heart surgery In the absence of an accurate measurement of actual blood loss the use of the blood pressure level as a guide to blood requirements is usually reliable in preventing overtransfusion. Nevertheless, a considerable volume of blood loss must occur before the blood presure declines and the pulse rate quickens. Thus to use a fall in blood pressure as the guide to transfusional requirements is not entirely satisfactory either. However, by and large, the blood pressure level is the indicator most often used clinically. We use it ourselves, though with the additional aid of a graduated suction trap bottle in which most of the lost blood is collected. Excessive transfusion leading to pulmonary edema or heart failure is further discussed on page 349.

REACTIONS DUE TO INCOMPATIBLE BLOOD. These are the most serious reactions and they are often fatal. They usually occur due to carelessness, and hence are rarely excusable: The nurse or intern on the ward fails to read the card: the anesthetist puts up a new bottle of blood with fatal haste when massive blood loss is occurring the technician fails to label blood for cross-matching immediately after it is drawn—all these circumstances may result in the transfusion of incompatible blood Incredible as it might seem, the writer once was present at a discussion of the technic and hazards of blood transfusion when, at the close of the hour, incompatible blood was started accidentally as a demonstration The nurse present had been given the blood by another nurse, and neither the instructor nor the nurse present had checked the blood against the patient's identity, the wrong blood was begun Fortunately scarcely more than 50 cc had gone in before the patient began to have various pains and developed a chill—at just about the time another nurse came running with the correct blood The needle was yanked out and, fortunately, the patient soon became afebrile and had no serious sequelae such as oliguria or anuria *Carelessness is the commonest cause of transfusion reactions.*

Even 50 cc of mismatched blood can produce a violent reaction that is followed by hemoglobinemia, hemoglobinuria, and renal shutdown. These phenomena are usually preceded by restlessness, anxiety flushing of the face, precordial oppression, tachycardia, and pain in the back and thighs If the patient is under general anesthesia, the shivering will of course be absent; however, there may be a *fall in blood pressure and excessive oozing.* The latter may be due in some cases to thrombocytopenia, associated with a degree of hypoprothrombinemia and hypofibrinogenemia. However, the rôle of shock in reducing the contractility of peripheral vessels is perhaps more important The initial leukopenia is followed by leukocytosis

The hemolytic effects of the patient's serum against the infused mismatched cells is quickly apparent as the free hemoglobin level in the serum of the recipient rises and hemoglobin is passed in the urine If the degree of incompatibility has been limited to the minor factors or if only a small amount of the mismatched blood has been given the entire clinical picture may subside in 24 hours, on the other hand it may proceed to uremia and eventual death The

mechanism involved in the production of lower nephron nephrosis appears to be that of a disruption of the renal tubule due to focal renal cortical ischemia hemoglobinemia *per se* is not a primary factor in producing the renal damage

Management of transfusion reactions due to incompatible blood The general management of renal shutdown was discussed on p 76 and need not be repeated here However certain specific points should be noted First, a transfusion should be stopped when the patient begins having a reaction—except perhaps in the highly exceptional circumstance when a degree of reaction is expected in the patient with a blood dyscrasia who has had multiple transfusions even here it is usually better to be safe than sorry Second, the remaining blood is returned to the laboratory promptly for rechecking and for culture to be certain that neither mismatched nor contaminated blood was given Third improperly stored blood may have contained excessive amounts of free hemoglobin or potassium, due to red cell hemolysis Fourth the probability of a degree of renal damage and oliguria should be anticipated and fluid intake adjusted accordingly The individual should be weighed and baseline plasma chemistry values should be obtained

Alkalinization of the urine has not been noticeably beneficial and has been generally discarded As stated above it is now believed that hemoglobin precipitation in the tubules is not a major factor in producing oliguria and the excess sodium given for alkalinization may render fluid control more difficult during the period of oliguria. A rigid intake-output record should be started just as soon as a serious transfusion reaction is suspected and the free hemoglobin levels of plasma should be followed over the next few hours.

Other Considerations in Transfusional Therapy

There has been the tendency to give more and more blood for more and more operations Of course if blood is actually required to treat oligemia it must be used On the other hand, the unnecessary use of transfusion subjects the patient to hazards that are not justified The routine cholecystectomy or thyroidectomy does not require a blood transfusion, and there is no point in exposing the patient to the possibility of a transfusion reaction or to *homologous serum hepatitis* Judiciously employed, blood transfusion is, in contrast, a cornerstone of modern surgical practice, and thoracic surgery and many abdominal operations would be impossible without it

The use of universal Type O blood is not without distinct hazards, as seen in Figure 95 This patient exhibited severe hemolysis,

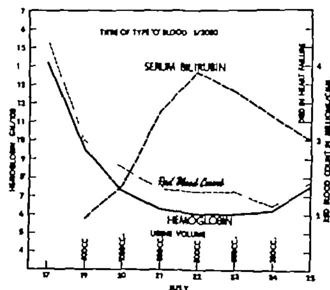


Fig 95 The use of universal Type O blood should be restricted to absolute emergencies

Hazards of using universal Type O blood. (D C., aged 73 385410 Wt. 77 4 kg. Type A Rh+) The rare but distinct risk of Group O blood administered to a patient of another blood group when the iso-agglutinin titer of Group O is excessive as illustrated graphically by the acute decline in the red cell count and hemoglobin concentration with concurrent development of icterus This is the so-called "minor" field or crossmatch wherein the incompatibility is that of the donor's serum for the patient's cells Note that in spite of the severe degree of hemolysis the daily urine volume was moderately good This is in contrast with the oliguric or anuric states which follow reactions wherein the cells of the donor are incompatible with the serum of the recipient. (From ALLEN J G In *Surgery—Principles and Practice* edited by Allen, J G., Harkins, H N., Moyer C A., and Rhoads, J E Philadelphia, J B Lippincott Company 1957)

but did not develop serious renal complications—in sharp contrast to the oliguria or anuria that usually follows the transfusion of blood wherein the cells of the donor are incompatible with the serum of the recipient Type O blood should be given to patients whose blood groups are A, B, or AB only when an emergency exists—as it not infrequently does

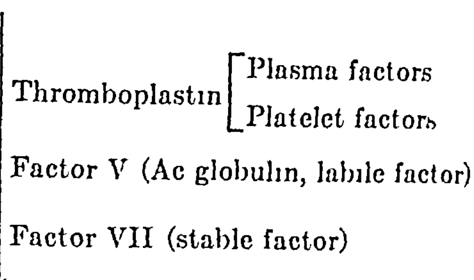
Blood Clotting and Coagulation Defects

Mechanism of Coagulation

The physiology of blood clotting is complex,[9] and the situation has not been improved by the large number of often conflicting publications that have appeared in recent years Too, the endocrine organs are being increasingly implicated in these processes [3,5] Fortunately, however, the essential features of the classic concept of coagulation still hold The newer advances have had to do with subfactors which promote the basic processes of the conversion of prothrombin to thrombin, and of fibrinogen to fibrin [6]

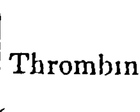
The following discussion will skirt the conflicts which rage among the coagulationists, in other words, this discussion is for those who are not specialists in the coagulation field Repetition and frequent cross reference are used to clarify A skeleton outline of coagulation is as follows [2]

1 Prothrombin



Thrombin

2 Fibrinogen



Fibrin

3 Clot Retraction

4 Fibrinolysis

In the above scheme, coagulation is initiated by contact of the blood with a "rough" surface Such contact triggers clotting by causing disintegration of platelets and release of the platelet lipoid thromboplastic factor, it also activates plasma thromboplastin component (PTC) as well as Factor VII, both of which circulate in an inactive form (Fig 96) Tissue injury yields thromboplastin directly The thromboplastin made available from these three sources now combines with Factor VII—stable factor, serum prothrombin conversion accelerator (SPCA)—to form a minimal amount of thrombin This initially formed thrombin then triggers the accelerator system Factor V (accelerator globulin, Ac globulin) is now activated, and Factors V and VII interact in the presence of calcium to form "prothrombinase" According to Wintrobe[24] this last substance, which also requires the presence of calcium, accelerates the conversion of prothrombin to thrombin Thus, thrombin is now present in sufficient quantity to convert fibrinogen to fibrin

This theory of the clotting mechanism is based largely upon the views of Owren and

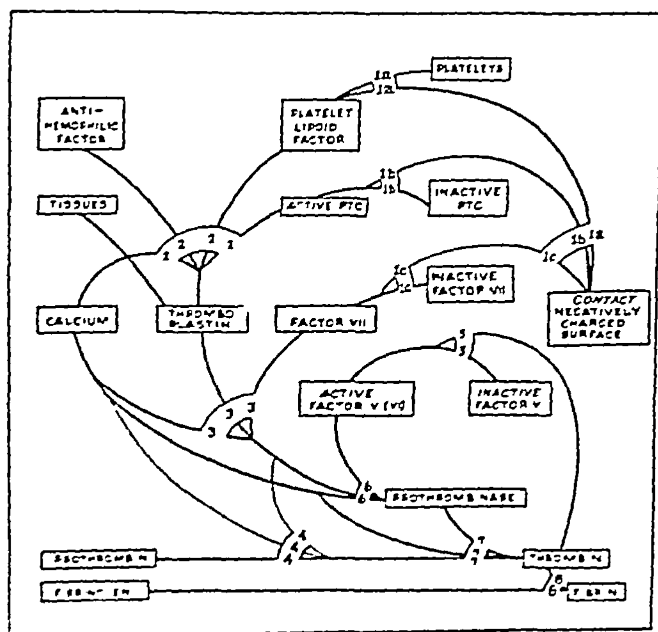


Fig 96 Owren's scheme of blood coagulation, as modified slightly by Wintrobe (see text) (From Wintrobe, M M *Clinical Hematology*, Ed 4 Philadelphia, Lea & Febiger, 1956)

his associates[17] and the steps are illustrated more elaborately in Figure 96 There are of course several other current theories, but it would serve no useful purpose to give them all. Let it be clearly understood that *all theories of blood clotting are tentative*, at least in part

Since the classic factors—prothrombin, thromboplastin, calcium, and fibrinogen—remain valid, it will be apparent that the newer knowledge of coagulation centers around the factors that, with thromboplastin are responsible for the conversion of prothrombin to thrombin among these are Factor V (Ac globulin, accelerator globulin, labile factor), Factor VII (stable factor, SPCA proconvertin convertin), and anti hemophilic globulin (AHG) Further clarification of the rôle of these factors in the clotting process may be achieved by inspection of the following scheme of Wintrobe [23]

First phase

AHG + platelets $\xrightarrow{\text{PTC}}$ intermediate product

Intermediate product +

Factor V $\xrightarrow{\text{Factor VII}}$ thromboplastin

Second phase

Prothrombin $\xrightarrow{\text{thromboplastin}}$ thrombin

Third phase

Fibrinogen $\xrightarrow{\text{thrombin}}$ fibrin

This conceptual outline was based upon the report of Biggs Douglas, and Macfarlane (Biggs, R Douglas A. S, and Macfarlane R G The formation of thromboplastin in human blood J Physiol **119**: 89 1953)

While there is disagreement concerning the need of platelets for initiation of the clotting process platelets ultimately contribute an important thromboplastin factor In addition the platelets are responsible for normal clot retraction.

AHG and Factor V are consumed during normal clotting their consumption preceding that of prothrombin which is also almost completely utilized

Physical and Chemical Properties of the Clotting Factors[2]

Prothrombin has the characteristics of a globulin and is contained in Cohn's Fraction III 2 Its molecular weight is about 140 000 and gradually disappears during storage in citrated plasma at +5 C

Thrombin is a protein with the characteristics of an albumin and has a molecular weight of about half that of prothrombin

Fibrinogen is of course a protein, with a molecular weight of about 400,000 It is contained in Cohn's Fraction I 2

Factor V (Ac globulin labile factor) is very sensitive to storage at room temperature or at +5 C, and under such conditions a great portion of its activity rapidly disappears

Factor VII (SPCA, proconvertin-convertin) decreases during treatment with Dicumarol, as may prothrombin Factor V does not. Factor VII is quite stable during storage whereas Factor V is not. For example Factor VII remains practically unaltered for 4 days at +25 to 37 C in stored serum. Therefore, since prothrombin and Ac globulin (Factor V) gradually disappear from the serum, it is possible to obtain a serum in which these two factors have been eliminated This is a useful point both in elucidating the deficient factor in clinical coagulation problems and in clinical therapy Prothrombin and Factor VII deficiencies can usually be corrected by administration of vitamin K_1 oxide Factor V does not respond as well to vitamin K_1 therapy, but it can be supplied on a temporary basis by freshly drawn blood (less than 4 days old)

Thromboplastin factors can be deficient, and hemophilia has been found to be due to a deficiency of a globulin that has since been called AHG (antihemophilic globulin) The addition of a small amount of this globulin to the blood of the hemophiliac temporarily returns the clotting time to normal. There

are other alleged factors (Fig 96), but it is desirable to preserve simplicity here in the pursuit of clarity

Calcium is important in several phases of the clotting process While varying the calcium concentration in the *in vitro* experiments can alter clotting significantly, we have never seen abnormal bleeding that was clearly due to hypocalcemia; in fact, one doubts that during life the serum calcium level ever falls so low as to preclude clotting

Natural Inhibitors of Blood Coagulation

Throughout this volume the elaborate system of checks and balances which exists in the body has been emphasized It would be surprising indeed if there were not present anticlotting factors which oppose those that promote clotting That is, *failure of the blood to clot may be due either to a deficiency of a substance required for coagulation (e g , thromboplastin components, prothrombin, Factor V, Factor VII) or to an excess of a circulating anticoagulant substance* Such a substance might resemble heparin and would oppose various of the coagulation factors Such substances do occur

If a coagulation defect is due to a deficiency of AHG, for example, it is correctible by the use of fresh normal plasma, if it is due to a natural circulating anticoagulant, on the other hand, the clotting time is not readily corrected by the addition of normal plasma in small amounts

Clot Retraction

It was noted earlier that normal clot retraction is dependent upon an adequate number of platelets If these are deficient the clot retraction is impaired, as seen in idiopathic thrombocytopenic purpura where capillary fragility and the bleeding time are also increased

Fibrinolysis

Fibrinolysis is an important aspect of the total coagulation mechanism, although acting on the final product, fibrin Fibrinolysin is contained in Cohn's Fraction III-3 In certain diseases, as with some prostatic cancers, the amount of circulating fibrinolysin is increased and serious bleeding may occur This is even more serious if an associated fibrinogen deficiency exists

Diagnosis and Treatment of Coagulation Defects in Surgical Patients

During most operations blood clotting is adequate and the surgeon hardly gives it a thought In some circumstances, however, defective clotting may occur (1) antecedent liver disease may have lowered the prothrombin level and the level of Factor VII (and Factor V), (2) Dicumarol therapy may have lowered the level of Factor VII (and prothrombin), (3) heparin therapy may have increased antithrombic activity, (4) mismatched blood may cause diffuse oozing (due to thrombocytopenia, hypoprothrombinemia, and hypofibrinogenemia?) (5) a history of "bleeding" may suggest a hemophilic type of individual (AHG deficiency), or (6) the need for massive transfusion may have lowered the platelet count to a critical level Should any of these circumstances exist, the surgeon should be alert to the possibility of excessive bleeding If anticoagulant therapy is indicated in a patient who may later require surgery, heparin is both more effective[22] and its effect more readily reversed than is that of Dicumarol

Unfortunately, the most serious complications due to coagulation defects are likely to be encountered unexpectedly during surgery, and under these circumstances the surgeon is often at a loss to explain the cause of the hemorrhagic diathesis Nevertheless, with the proper tests the defect can usually be identified, and reasonably effective therapy employed [7] A few of these tests will now be reviewed, but for the finer details the reader is referred to the monographs noted in the bibliography That of De Nicola[2] is especially helpful, and various parts of this discussion have been gathered from it

STEPS IN IDENTIFYING A COAGULATION DEFECT First, the *whole blood clotting time* should be performed The most common causes of a prolonged clotting time are (1)

hemophilic syndromes (e g , AHG or PTC deficiency) (2) endogenous circulating anticoagulants (e g antithrombin or anti thromboplastin) (3) exogenous anticoagulants (e g heparin) and (4) hypofibrinogenemias (e g , during difficult or complicated labor, various operations)[18, 19]

The steps that may be followed in identifying which of these various possibilities is actually the cause of the prolonged whole blood clotting time are shown in Figure 97 Suffice it to state again that small amounts of fresh normal plasma can decrease the clotting time of an hemophilic plasma but not the clotting time of a plasma containing anticoagulants Further tests are required to identify specific offenders in these groups The laboratory methods used in identifying deficiencies of the other factors in Figure 98 need not be detailed here

The *apparently normal clotting time* is a relatively new concept, but it is now accepted that the whole blood clotting time can be normal or only slightly prolonged when in fact, a definite coagulation defect does exist (Fig. 98)

In general, as pointed out earlier coagulation defects are due either to a *deficiency* of one or more factors required for clotting or to an *inhibition* of one or more such factors Thus, there may be deficiencies of the following

1 Thromboplastin (a) Platelet thromboplastin deficiency due to *thrombocytopenia* or to qualitatively abnormal platelets (*thrombocytopathies*) (b) AHG as in hemophilia This is a plasma thromboplastin factor in contrast to platelet thromboplastin factor

2 Prothrombin Factor V and Factor VII These deficiencies are especially apt to be encountered in liver disease and in congenital hypoprothrombinemia

3 Fibrinogen Afibrinogenemia or hypofibrinogenemia may be met in the presence of obstetrical complication or following surgery especially operations upon the lungs pancreas and prostate The defect is manifested by a failure of blood to clot or to clot satisfactorily The application of topical thrombin will produce clotting in the blood specimen if fibrinogen is present.

Inhibitors of clotting are, as noted above, the circulating anticoagulants which oppose various of the clotting factors In addition, alterations in fibrinolysis are important, for numerous reports have appeared in recent years to indicate the importance of increased fibrinolysin activity in producing an hemorrhagic diathesis

Diggs[4] has stressed the importance of the prothrombin time (Quick s one stage method) in the rapid screening of hemorrhagic diseases Whereas this test is normal in the hemophiliac diseases, it is prolonged in deficiencies of prothrombin, Factor V, and fibrinogen, and where excess anticoagulants are present in the blood. More selective studies are required to identify the defect more precisely

Management of Postoperative Bleeding

1 Exclude unligated vessels *The most common cause of a postoperative bleeding diathesis is that of inadequate technical hemostasis at surgery* If the blood clots and the platelet count is normal, suspect inadequate technical hemostasis

2 Massive blood transfusion may produce marked thrombocytopenia[10] Further blood transfusion may only aggravate the condition. Plasma transfusion can be used to sustain blood volume allowing the platelet count to rise A transfusion of platelets if available is helpful[20] Fresh blood is useful

3 Deficiencies of prothrombin and Factor VII are usually corrected by vitamin K_1 oxide if adequate liver function remains A deficiency of Factor V will not be affected by vitamin K_1 but will be improved by fresh plasma or blood transfusion (less than 4 days old) Dicumarol effects are reversed by K_1 oxide [1]

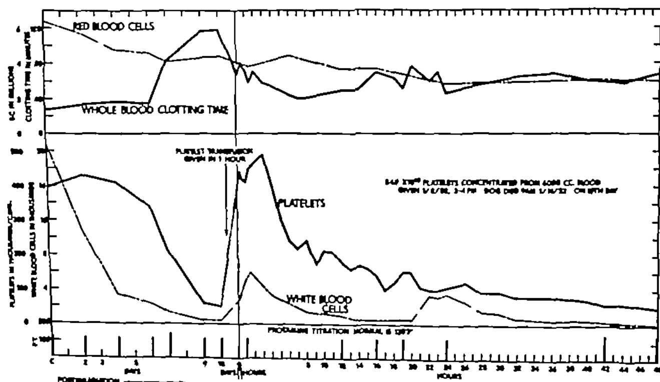
4 Plasma thromboplastin deficiency[8] (in contradistinction to platelet thromboplastin) can be improved by whole blood or plasma transfusion or by the administration of a plasma concentrate containing AHG if available (Fig. 99)

Causes of Alterations in the Various Measures of Coagulation

Laboratory Finding	Condition	Mechanism and Pathogenesis
I *Coagulation time* prolonged	A Hemophilia	Deficiency of anti-hemophilic globulin (AHG)
	B PTC deficiency	Deficiency of plasma thromboplastin component
	C PTA deficiency	Deficiency of plasma thromboplastin antecedent
	D Hyperheparinemia	Excess heparin or heparinoid substances (heparin therapy, anaphylactic and peptone shock)
	E Idiopathic	Excess anticoagulants of unknown type
	F Afibrinogenemia and hypofibrinogenemia	Deficiency of fibrinogen, various causes, congenital and acquired
	G "Hypoprothrombinemia"	When "prothrombin" is less than 10 per cent of normal May be due to lack of prothrombin, factor V or factor VII
II *Prothrombin time* (one-stage) prolonged	A Excess Dicumarol or related therapeutic agent	Deficiency of prothrombin and factor VII
	B "Parahemophilia"	Factor V deficiency
	C SPCA deficiency	Factor VII deficiency
	D Vitamin K deficiency	In newborn (hemorrhagic disease of the newborn) and whenever absorption of vitamin K is impaired
	E Liver disease	Impaired formation of prothrombin and factors V and VII
III *Prothrombin consumption* reduced	A AHG, PTC, or PTA deficiency	Impaired thromboplastin formation
	B Thrombocytopenia	Impaired thromboplastin formation
	C "Thrombasthenia"	Impaired thromboplastin formation
	D Circulating antithromboplastin	Impaired thromboplastin formation
IV *Bleeding time* prolonged	A Thrombocytopenic purpura	Platelet deficiency
	B Any of the causes under I or II if sufficiently severe	Extreme poverty of blood and tissues in coagulation factors
	C von Willebrand's dis e	Abnormality of capillaries of skin and mucous membranes
V *Tourniquet test* positive	A	amage to capillary endothelium
		lets too few to support pressure
		ular ce-
		ry-
VI *Thrombocytopenia*		
VII *Clot retr* poor		

	Test	Defect
Apparently normal whole blood clotting time	Prothrombin time	Hypoprothrombinemias Factor VII deficiency Ac-Globulin deficiency
	Clotting time in siliconed test tubes	Hypoprothrombinemias Factor VII deficiency ? Ac Globulin deficiency ? Antithromboplastinemia
	Fibrinogen determination	Fibrinogenopenias
	Platelet count	Thrombocytopenias Thrombocytopathies
	Prothrombin utilization	Mild hemophilia Hemophilia after transfusions Thrombocytopenias Thrombocytopathies Ac-Globulin deficiency
	Heparin tolerance *in vitro*	Mild hemophilia Hemophilia after transfusions Thrombocytopenias Thrombocytopathies Hypoprothrombinemias Factor VII deficiency Ac Globulin deficiency

Fig 98 Tests for identifying coagulation defect when whole blood clotting time is apparently normal or only slightly prolonged (DE NICOLA P *The Laboratory Diagnosis of Coagulation Defects.* Springfield Ill., Charles C Thomas, 1956)



Platelet transfusion. Illustrating the rapid declines in platelet count after platelet transfusions. Animals were rendered thrombocytopenic by total body radiation.

Fig 99 Platelet transfusion This technic is now available for clinical use Platelets furnish a thromboplastic factor and are responsible for clot retraction (From ALLEN J G In *Surgery—Principles and Practice* edited by J G Allen H N Harkins C A. Moyer and J E. Rhoads. Philadelphia J B Lippincott Company 1957)

5. Bleeding due to "heparin-like" substances may respond to protamine sulfate injection (as does bleeding due to injected heparin) and whole blood transfusion
6. Hypofibrinogenemia is best treated with intravenous fibrinogen and whole blood transfusion Treatment must be vigorous, and many liters of blood may be required
7. Bleeding from exposed surfaces may respond to topical thrombin application if sufficient fibrinogen is present. Conversely, if the addition of thrombin does not produce clotting there is probably a fibrinogen deficiency.
8 Calcium is rarely required. Patients in prolonged shock may hemorrhage not only because of various *deficiencies* but also because of circulating *anticoagulants*

Splenic Dysfunction

Functions of the Normal Spleen

For many years the functions of the spleen were an enigma despite the fact that splenectomy was known to be followed by certain characteristic changes in the peripheral blood picture of normal subjects Even at the present time the functions of this organ are obscure, but knowledge has progressed to a point that permits a somewhat more physiologic approach to therapy.

The spleen has been termed an enormous lymph node interposed between an artery and a vein [1] The splenic artery is the largest branch of the coeliac axis, and the splenic vein is the largest tributary to the portal system The organ varies much in size and, by virtue of its muscle elements, it contracts promptly upon the injection of epinephrine or stimulation of the sympathetic nervous system. Red cells are stored in the spleen, to an extent, and older cells or spherocytes concentrate there and become destroyed, their hemoglobin is converted to bilirubin by the reticuloendothelial cells

Splenectomy results in an increase in the number of red cells white cells, and platelets in the peripheral blood (Fig 100). For example, splenectomy performed because of accidental splenic trauma may result in a rise in the red cell count of 0 5 million, a leukocytosis of 12,000 and a platelet count rise from the normal level of approximately 400 000 to 1,000,000 Indeed, some surgeons give anticoagulants if the platelet count rises above 800,000 in the days following splenectomy—the stated purpose being to prevent thrombotic phenomena Another phenomenon of interest is that following a "clean splenectomy many patients run a fever for from 7 to 10 days. This has never been explained to our satisfaction but many have assumed that it is due to a 'propagating thrombosis in the ligated splenic vein '

Dameshek and Welch[1] concluded, from data obtained following splenectomy that the spleen not only assists in the regulation of the peripheral blood picture by acting upon the cells that enter its confines but that the spleen also elaborates humoral factors or "hormones' that control the growth, maturation, and rate of release of the blood elements in bone marrow and lymphoid tissue They emphasized the relation of other endocrine elements—hypothalamo-pituitary apparatus, adrenal cortex. thyroid and sex

PHYSIOLOGY

EFFECTS OF SPLENECTOMY

A good way to study an organ's function is to note effects of its removal
Splenectomy causes many changes in the blood cells:

BLOOD COUNTS — CONCLUSIONS-

	Splenectomy Before	Splenectomy After	
RBC ↑	5.0 M	5.5 M	Spleen controls to some extent the growth and emission of the bone marrow blood cells
WBC ↑	7000	15000	
Platelets ↑	400000	1000000	

RED CELLS

1. Target cells (leptocytes) thin
   Increased hypotonic resistance
2. Howell-Jolly bodies
   Occasional nucleated red cells
3. Diminished red cell destruction
   hemolytic index diminished

Spleen makes red cells thicker
Controls their denucleation
May modify their life span
Partakes in hemoglobin destruction

WHITE CELLS

	Splenectomy Before	Splenectomy After	
WBC ↑	7000	15000	Spleen regulates Granulocytopoiesis and Lymphocytopoiesis
Polys. ↑ or same	70% 5000	50-60% 7500-9000	
Lymphs. ↑	20% 1400	40-50% 6000-7000	

PLATELETS

	Before	After	
Plts ↑	400,000	1,000,000	Spleen controls or regulates platelet production by megakaryocytes

GENERAL CONCLUSION Spleen probably produces humoral factors acting upon bone marrow and lymphoid tissue

Fig. 100. Splenectomy is often followed by definite fever for several days (From DAMESHEK, K. AND WELCH, C. S. *Hypersplenism and Surgery of the Spleen* New York. Grune & Stratton. Inc. 1953)

hormones—to bone marrow and lymphoid tissue function In addition to the evidence derived from splenectomy, the fact that x ray destruction of the bone marrow in rats is diminished by shielding the spleen with lead has also been offered as evidence that the spleen contains an humoral factor that protects bone marrow

In abnormal splenic conditions affecting the peripheral blood—as may occur naturally in human beings or may be produced experimentally by ligation of the splenic vein—one of two processes, or both, may come into play Either the spleen may harbor larger numbers of cells that are then destroyed or, some splenic hormone may inhibit the bone marrow

Hypersplenism[24]

There are numerous indications for splenectomy Among these are traumatic rupture, accidental tear of the splenic capsule during gastric resection, or its removal during *en bloc* dissection for gastric, colonic, or pancreatic cancer Nevertheless we are interested here in the diseases that are associated with an increased splenic function or activity Such diseases are manifested by thrombocytopenia, anemia neutropenia or pancytopenia (*Fig 101*) It was seen above that this may result from either an increased destruction of blood elements within the spleen or from the elaboration of an humoral substance by the spleen that inhibits bone marrow hematopoiesis

PRIMARY VERSUS SECONDARY HYPERSPLENISM. Before individual diseases are considered it is useful to distinguish between the terms primary and secondary hypersplenism The term *primary hypersplenism* designates hypersplenism that appears to be due to disease that originates in the spleen itself, or perhaps in conjunction with abnormal bone marrow red cell formation as in

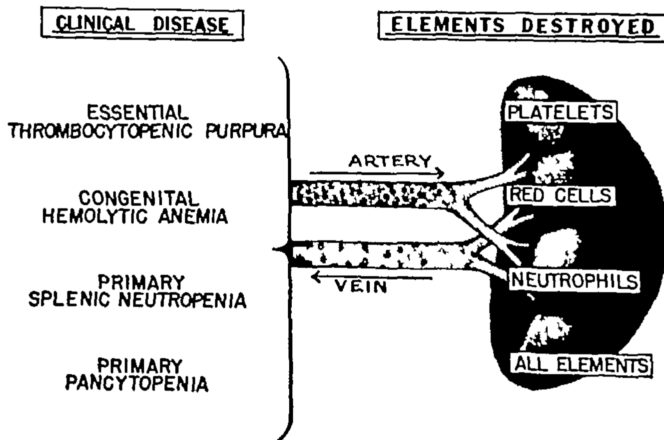


Fig 101 Schematic representation of one mechanism of hypersplenism (primary) The clinical syndrome is dependent on the blood element or elements destroyed There are those who believe that the spleen secretes a hormone which depresses the bone marrow in addition to possible increased cellular disintegration in the spleen itself (From ZOLLINGER, R M MARTIN M M AND WILLIAMS, R. D Surgical aspects of hypersplenism J A M A 149; 24 1952)

congenital hemolytic anemia The term *secondary hypersplenism* refers to derangements in the peripheral blood picture that result from splenic congestion secondary to a variety of systemic diseases In primary hypersplenism the spleen may at times be essentially normal in size In secondary hypersplenism the spleen is characteristically enlarged, and it is assumed that at least a major factor in the destruction of various blood cells is the cells' prolonged contact with the sinusoids of the large spleen Finally, in some patients the differentiation between primary and secondary hypersplenism is not easily made

FURTHER CAUSES OF HYPERSPLENISM It has been emphasized that many conditions that result in an enlarged spleen may produce a secondary hypersplenism A most common offender is portal hypertension, but sarcoidosis, tuberculosis, Gaucher's disease, Hodgkins' disease, and leukemia, if they involve the spleen, may also produce one or more of the manifestations of hypersplenism, including thrombocytopenia In contrast, there are several "splenic" diseases in which the histologic picture of the spleen may be that of hyperplasia In one of these, idiopathic thrombocytopenic purpura, the spleen is rarely enlarged The other "diseases" are congenital hemolytic anemia, neutropenia, and pancytopenia Splenectomy is often performed for these conditions, usually with clinical cure

Idiopathic thrombocytopenic purpura [16] This condition is usually encountered in young girls and in young adult women There is often a history of repeated episodes of spontaneous bleeding and subcutaneous ecchymoses To be sure, some patients have transient attacks of thrombocytopenic purpura, in some instances due to demonstrable allergy or infection, which are followed by complete and permanent remissions of the thrombocytopenia Adrenocorticotropic hormone (ACTH) or corticosteroid therapy is often useful in such patients, it may also be helpful in the acute attacks of patients who have the chronic disease, or in preparing these individuals for splenectomy However, when the disease has become chronic, splenectomy is the treatment of choice, and steroid therapy is of only temporary benefit

The *diagnosis* is established by the history of repeated bleeding and ecchymoses, a positive tourniquet test indicating increased capillary fragility, and a clot that is friable and retracts poorly (It will be recalled that normal capillary fragility and clot retraction require normal numbers of blood platelets) The platelet count is low The whole blood clotting time is usually normal by the more gross tests, but a coagulation defect can be demonstrated by the more stringent tests of whole blood clotting time or by the prothrombin consumption test (Figs 97 and 98) The bleeding time (in contrast to the gross clotting time) is prolonged The leukocytes are usually *normal in number and in* appearance

Although the platelet count is usually substantially reduced, in some circumstances the platelets may be normal in number but abnormal in behavior (thrombocytopathy), producing a coagulation defect This is not rare but it need not further concern us here The level of the platelet count at which spontaneous bleeding occurs varies considerably from patient to patient As a rule, though, bleeding will occur if the platelet count falls below 60,000 per cu mm (platelet counts notoriously have a considerable range of error in most hospital laboratories)

Bone marrow studies are essential in all blood dyscrasias to rule out primary disease of the marrow [15] In thrombocytopenia, for example, it is important to exclude primary or hypoplastic anemia, leukemia, metastatic carcinoma, and other conditions If active bone marrow thrombocytogenesis is reflected in normal or increased numbers of megakaryocytes, then one can more confidently assume that hypersplenism is the cause of the thrombocytopenia (by suppressing megakaryocyte maturation) [1] Also, one can more confidently predict that the patient will be improved by splenectomy.

Results of splenectomy —If other demonstrable causes of thrombocytopenia have been excluded, leaving the residue of "idiopathic' thrombocytopenic purpura cases, these will be benefited by splenectomy in the majority of instances Whereas it is often necessary to transfuse the patient with *fresh blood* to supply platelets for adequate coagulation until the splenic artery can be clamped once this vessel is occluded the platelet count in the peripheral blood begins to rise almost immediately Subsequent spontaneous bleeding is not often a problem, though occasionally further transfusions to supply platelets are needed in the immediate postoperative period

Typically, the platelet count may rise postoperatively from a preoperative level of perhaps 60,000 to perhaps 600,000—but usually not to above 1,000,000, as often happens following removal of a normal spleen at gastric resection Thereafter the platelet count gradually declines to a normal level of perhaps from 300 000 to 500 000 (normal 400 000) and further hemorrhage does not occur The following case study illustrates many of these points

Patient D R a 21 year-old white woman (Fig. 102), was admitted to the University Hospital on March 19, 1956 with the chief complaint of spitting up blood Questioning revealed that she had first bled from her nose and mouth when she was 8 years old the free and visible bleeding being accompanied by many "bruise marks' over her body The following year this had recurred and again when she was 10 At one time she had been given transfusions for nose bleed, but these had caused such "shaking spells of her body that further transfusions were avoided Surprisingly enough, after menstruation had begun at about the age of 11 the number and severity of the bleeding episodes had diminished markedly according to her mother In fact, after the menarche there had been no further serious blood loss even when teeth were pulled until the current attack. One day prior to admission she had begun to bleed from her gums and

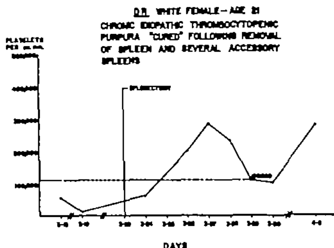


Fig 103 Patient had had episodes of spontaneous hemorrhage and ecchymoses since age 11 (but ameliorated by menarche) She had no further objective findings post-splenectomy However the platelet count was still subnormal Idiopathic thrombocytopenic purpura is more common in young females than in males Graph shows platelet counts before and following splenectomy (see text)

noticed that numerous ecchymoses were appearing over the body There was no history of infections or drugs that might have served as precipitating factors

Past history disclosed that she had delivered two normal children without incident, one now 4 years and one 12 months of age This was of particular interest because the mortality among pregnant women who have idiopathic thrombocytopenic purpura has been reported to be relatively high

Physical examination revealed many petechiae widespread purpuric spots, and a positive tourniquet test Neither the liver nor the spleen was palpable as was to be expected if the presumptive diagnosis of idiopathic thrombocytopenic purpura was correct.

Hematology consultation and studies showed an *abnormal coagulogram* The platelet count was 54 000 per cu. mm. with no prothrombin consumption or clot retraction The one-stage prothrombin time was prolonged due to a reduction in Factor VII It was pointed out that a reduced Factor VII is a common finding during active bleeding

The *iliac bone marrow* was readily aspirated, and revealed a normal cellularity The megakaryocytes were numerous but

about 80 per cent were immature Both red and white cells were plentiful and were maturing normally Thus, primary bone marrow hypoplasia was eliminated as the cause of the thrombocytopenia, focusing attention upon the spleen The opinion of the hematologist was that "this would appear to be a classical case of idiopathic thrombocytopenic purpura (spleen not palpable) This is her fourth attack since the age of 8 years Although it is impossible to prove that the other episodes were due to thrombocytopenia, I think we should classify her as chronic Treatment would seem to lie between corticoids or splenectomy I personally would favor the latter course as this would be more likely to produce a permanent cure "

At operation on March 23, 1956, following ACTH therapy of 24 hours' duration, a spleen of normal size and several accessory spleens were removed uneventfully

The *postoperative platelet counts* are shown in Figure 102 From a level of 26,000 two days prior to operation the count rose progressively to 280,000 on the fourth postoperative day, followed by a gradual decline to 100,000 on the seventh postoperative day In follow-up clinic on April 6, 1956 (thirteenth postoperative day) the platelet count was 277,000 She has remained well since

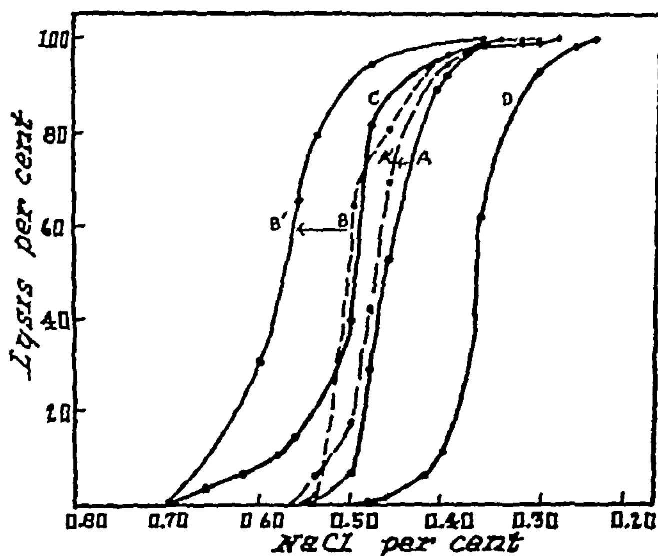


Fig 103 Note variations in red cell fragility in different blood dyscrasias Normal and abnormal osmotic fragility curves *A*, Normal curve, *A'*, the moderate increase in osmotic fragility on incubation *B*, Hereditary spherocytosis, *B'*, greatly increased osmotic fragility following incubation *C*, "Acquired" hemolytic anemia *D*, Increased resistance of red corpuscles from a case of Thalassemia minor (From WINTROBE, M M *Clinical Hematology*, Ed 4 Philadelphia, Lea & Febiger, 1956)

Congenital hemolytic anemia This disease has also been variously termed hereditary spherocytic anemia, chronic acholuric (no bile in urine) jaundice, familial hemolytic icterus, and hereditary globe cell anemia This variety of names characterizes five major manifestations of the condition (1) the hereditary trait which usually causes the disease to be present early in life, (2) hemolysis, (3) jaundice without bile in the urine, (4) the increased numbers of spherocytes, and (5) anemia

The severity of the disease varies greatly One patient may suffer repeated and serious hemolytic crises whereas another may be "more yellow than sick" Multiple small black gallstones develop in more than half the patients In fact, the youngest patient upon whom the writer ever performed cholecystectomy (after prior splenectomy) was a girl 7 years old who had gallstones due to congenital hemolytic anemia *The spleen is usually enlarged*

Laboratory data reveal the characteristic increase in spherocytes in the peripheral blood, and these cells show increased fragility to hypotonic solutions and mechanical trauma (Fig 103) The reticulocyte count is usually *increased, falling to normal levels* following splenectomy The bone marrow reveals normal or increased erythropoietic activity

The diagnosis is established on the basis of the history, splenomegaly, laboratory data, and the exclusion of other conditions with which the disease might be confused, such as other causes of jaundice, anemia, or splenomegaly

Splenectomy is the treatment of choice In most patients the anemia and the jaundice disappear, but the spherocytosis and the consequent increased fragility persist That is, the underlying hereditary marrow

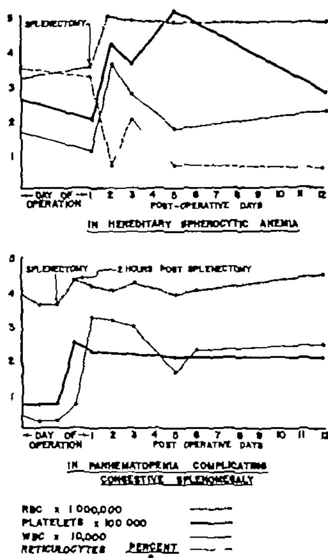


Fig 104 Hematologic effects of splenectomy In hereditary spherocytic anemia (congenital hemolytic anemia) the platelet, leukocyte and red cell counts rose after splenectomy the reticulocyte count fell In panhematopenia secondary to congestive splenomegaly the platelet leukocyte and red cell counts all rose after splenectomy (After MacKenzie, D W Jr., and Lowenstein L. In Moseley s *Textbook of Surgery* Ed 1 St. Louis, C V Mosby Company 1952)

defect which results in excessive numbers of spherocytes is not changed by splenectomy, but the dissolution of these cells in the spleen is abolished.

Immediately after splenectomy the red cell count begins to rise and the reticulocyte count begins to fall (Fig. 104) As with splenectomy in other circumstances the leukocyte and platelet counts rise also, but they gradually subside to the normal level present preoperatively

Neutropenia and pancytopenia These conditions are encountered in both primary and secondary hypersplenism Following splenectomy the anemia, neutropenia, and thrombocytopenia of primary hypersplenism may be considerably improved (Fig 104) The results are often less satisfactory in secondary hypersplenism, usually because of the underlying hepatic cirrhosis or other conditions

Splenic anemia due to chronic congestive splenomegaly (Banti s syndrome) is but another name for secondary hypersplenism due to *portal* hypertension

SPLENECTOMY IN OTHER CONDITIONS. Upon occasion splenectomy may be helpful in selected cases of Hodgkins' disease, leukemia lymphosarcoma or other conditions in which splenomegaly is contributing to the genesis of anemia The operation cannot cure the underlying disease, but it may diminish the number of transfusions required —a matter of considerable importance when a patient with a chronic blood dyscrasia has begun to exhibit reactions to blood from any donor Yet splenectomy should be resorted to with the full realization that it may not even diminish the blood requirements

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Chapter 14

The Alimentary Tract

The Salivary Glands

The salivary glands are important because of the saliva they secrete and because of the fact that they may be subject to inflammatory changes, injuries, tumors or to the formation of calculi (Fig. 105)

NERVOUS INFLUENCES The salivary glands—parotid, submaxillary, and sublingual—are under the control of both the sympathetic and the parasympathetic nervous systems (Fig 258) The stimulation of either nerve supply alters the secretion of the organ stimulation of the sympathetic supply produces saliva which is thick and scanty, whereas stimulation of the parasympathetic supply results in a watery but copious flow As with the stimulation of the nerve supply to the pancreas (which structure may also be involved in mumps and which also secretes amylase) the effect of sympathetic stimulation probably is mediated largely through vasoconstriction, and one would thus expect that the volume of the secretion would be diminished. Although the flow of saliva is regulated largely by nervous impulses many different types of stimuli may bring about salivation among these are the taste sight thought or smell of food mechanical manipulation within the mouth cerebral seizures and other factors

The *function* of the saliva has largely to do with mechanical and digestive processes The liquid aids in the mastication and swallowing of food. It helps to cool hot food and to dilute irritants. Moreover as most public speakers are aware it facilitates speech for it is difficult to enunciate clearly when the mouth is dry In addition, the enzymes of saliva initiate the digestive process, as in the partial hydrolysis of starch by ptyalin However, the digestive action of saliva is not great and is readily dispensed with

VOLUME OF SALIVA. The daily volume of saliva is approximately 1500 ml, and the secretion can present a problem of some magnitude when a salivary duct is severed by trauma, or blocked by stone, inflammation or fibrous stricture or when the patient cannot swallow the saliva, as following oral cancer surgery or in the presence of esophageal obstruction by tumor or stricture or congenital atresia or when a large tracheo-esophageal fistula permits flow of swallowed saliva into the lungs to produce pneumonitis The duration and prognosis of salivary drooling will depend upon the lesion lip defects can be closed, but the paralysis caused by bulbar brain lesions will usually be permanent

A most troublesome *salivary fistula* is that which follows a major laceration of Stenson's duct (Fig 105) Whereas smaller parotid fistulas will usually close with external pressure and patience, drainage from a severed main duct may continue until the duct is repaired, or until the proximal end is implanted into the oral cavity, or, as a last resort, until the gland is resected A submaxillary gland is, of course, easily excised

Atropine or Banthine may be used to reduce the volume of saliva temporarily, but this therapy is not satisfactory over a long period of time

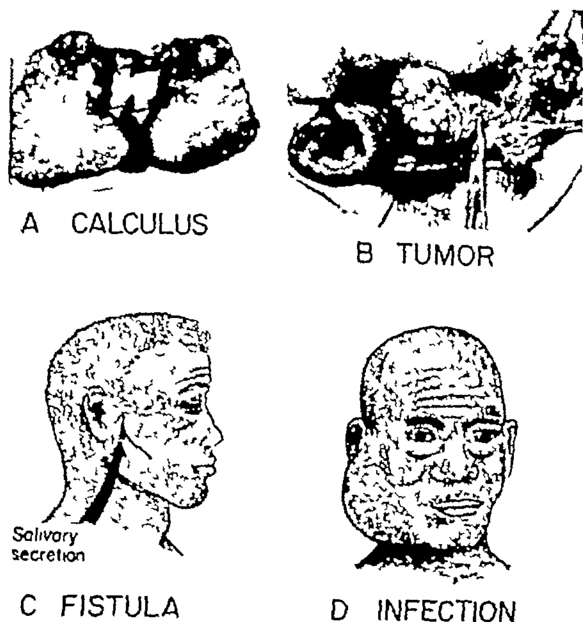


Fig 105 Diseases of the salivary glands *A* Excised submaxillary gland showing calculi The patient had lost weight simply because food stimulated the gland to secrete with resulting pain The submaxillary gland was easily removed Note chronic scarring surrounding the calculi in the ductal system *B* Parotid tumor and facial nerve The facial nerve has been exposed below and in front of the ear and it extends forward beneath the encapsulated tumor The hemostat has been passed beneath the nerve as it courses between the superficial half (retracted by rake) and the deep half (represented by tumor) of the parotid gland Total parotidectomy was performed with preservation of the nerve *C* Traumatic parotid duct fistula These lesions usually close in time If not, repair or excisional surgery is indicated *D* Infection Infections of the lower portion of the parotid gland are often difficult to differentiate from various tumors or tooth infections

Salivary calculi (sialolithiasis) are most frequently encountered in the ducts of a submaxillary gland, in our experience, and occasion discomfort chiefly by obstructing the flow of saliva at mealtime A common complaint is that of painful enlargement of the involved gland at the approach of food Indeed, so sharp may be the pain that the individual avoids food and may thus lose weight (Fig 105), between meals there is usually little discomfort

The calcium stones are usually visible on roentgen examination, and since infection and fibrosis often attend or occasion the stone formation, the most expeditious treatment is to excise the involved submaxillary gland, if this is the gland involved Care is taken to avoid injury to the lingual nerve and to the mandibular branch of the facial nerve In the case of parotid duct calculi the stone is removed without excision of the gland, if possible Roentgen therapy has been suggested to diminish salivary secretion in the presence of obstruction, but we have not used it

The Esophagus

General Remarks

The principal function of the esophagus is to carry food from the pharynx to the stomach, and the act of swallowing is the most important single kinetic function of this organ It is not surprising, therefore, that *dysphagia*—pain or other difficulty on swallowing—is the major symptom of esophageal disease The initiation of swallowing is under voluntary control, but thereafter the propagation of the bolus is involuntary Before food or fluid can enter the stomach the *cardiac sphincter* must be relaxed Though the mechanism by which the sphincter is opened is not clearly understood, most observers consider it to be under autonomic nervous system control, at least in part

The wall of the esophagus consists of three layers—the mucosa, the submucosa, and the outer (muscle) layer Unlike other parts of the alimentary canal, the esophagus has no serosal covering, moreover, its strongest layer is the mucosa, in contrast to the seromuscular layer of the intestine It is lined with stratified squamous epithelium, and esophageal carcinoma is of the squamous type, while that of the stomach and intestine is of the glandular type The blood supply of the esophagus has a segmental character, and only limited mobilization of the organ is possible without serious risk of necrosis and leakage at the line of anastomosis

SENSATION The mucosa of the normal esophagus is sensitive to heat and cold, but is insensitive to tactile stimuli In the

esophagus proper, pain is dependent upon tension of the muscular wall by either distention or spasm The pain may be burning in type when the stimulus acts continuously, and gripping when it is intermittent and intense Moreover, the patient can often identify the approximate location of the esophageal obstruction by reference to the point on the thorax at which he feels pain The mechanism of pain in esophageal peptic ulceration is considered to be similar to that of gastric and duodenal ulcer (*see below*), and the points of reference on the body surface to which pain from the esophagus is referred are innervated by branches from the IIIrd cervical to the VIIth or VIIIth dorsal spinal segments The sympathetic nerves provide the chief sensory pathways and although the vagi may contain some sensory fibers conclusive proof of this is lacking. The distress produced by esophageal spasm or the pain of hiatal hernia may radiate from the substernal area into the left shoulder and arm and thus simulate anginal pain. The sensation of pain caused by a hiatal hernia probably is transmitted over the phrenic nerve or the nerves of the lower part of the thorax. Heartburn is usually caused by a reflux of gastric juice into the esophagus and may be particularly distressing when the cardiac sphincter has been resected as for carcinoma of the lower third of the esophagus However the sensation may also be produced by distention of the lower esophagus or by stimulation of the mucosa of the cardiac portion of the stomach [7]

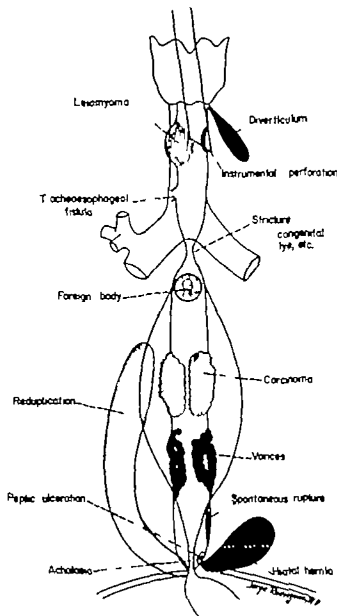


Fig 106 Esophageal lesions The efficiency of normal esophageal function is best appreciated when it has been lost When saliva cannot be swallowed and food cannot be ingested the patient seeks relief

Esophageal Diverticulum

In the composite presented in Figure 106 a cervical esophageal diverticulum is depicted. This outpouching occurs at the juncture of the lower pharynx and the cervical esophagus usually on the left. Diverticula may also develop in the mid esophagus at the level of the carina or just above the diaphragm. The condition is rarely encountered before middle age

As the diverticulum gradually enlarges and forms a dependent sac when the patient is upright ingested materials tend to enter the defect and to become stagnant and putrid. This gives rise to a most offensive odor which together with loudly audible gas gurgles often leads the sensitive patient to avoid social contact Even so at this stage the most serious problem associated with the diverticulum is the inability of the individual to lie down without strangling from the fluid that flows out of the diverticulum and into the trachea. This aspiration produces chronic pneumonitis that is

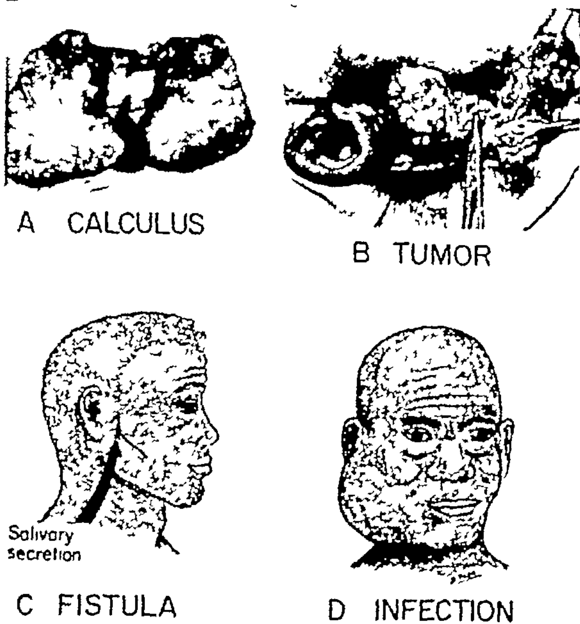


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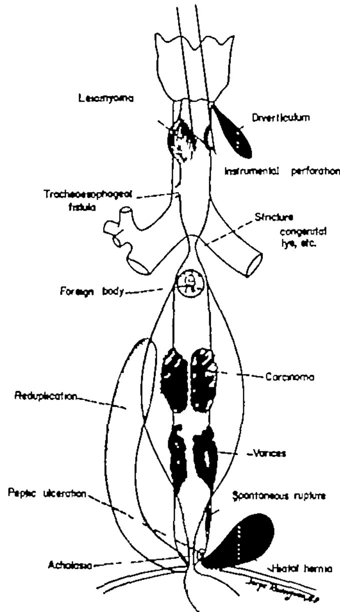


Fig 106 Esophageal lesions The efficiency of normal esophageal function is best appreciated when it has been lost When saliva cannot be swallowed and food cannot be ingested the patient seeks relief

readily visible on roentgenogram, and many of these subjects learn to sleep in a semi-erect position

Eventually the diverticulum may become so large, contain so much material, and so distort the esophagus as to render it impossible for the patient to ingest adequate amounts of food Chronic starvation ensues, and these subjects may be among the most emaciated that one will encounter in practice, if individuals with incurable disease be excluded

Treatment consists of improving the nutritional status with blood transfusion, intravenous alimentation, and, if possible, by means of a polyethylene tube passed at esophagoscopy Abrupt hyperalimentation is to be avoided, for it may result in sudden death We repair the diverticulum in one stage, frequently under local anesthesia if it is in the neck

Caustic Stricture

The ingestion of very hot or caustic materials produces a violent inflammatory reaction of the mouth, pharynx, and cervical esophagus, and at times it may extend almost to the stomach During the first two weeks the mucosa and underlying tissues are friable and edematous, but thereafter fibrous stricture of the esophagus often develops We feel that cautious esophageal dilatation should be initiated at the end of from 10 to 14 days, aided by a gastrostomy for feeding purposes But whatever the therapy, these patients may have a long and difficult course ahead of them, and often for life Various forms of esophageal substitutes have been attempted—stomach, small bowel, large bowel, skin flaps, and synthetic prostheses —but almost every successful such case has been considered reportable, reflecting the relative rarity with which corrective surgery is truly successful

Tracheoesophageal Fistulas

Communications between the trachea or a major bronchus and the esophagus are usually congenital, neoplastic, traumatic, or, less commonly, infectious in or all instances the immediate probl diminish the flow of saliva and ot terial from the esophagus through th and into the lungs In general, the r congenital fistulas in the newborn sl attended by less than 50 per cent m Traumatic fistulas, if small, will oft with adequate drainage and su management Direct surgical attack may not be successful, but it shoul tempted if prolonged conservatism avail Neoplastic fistulas usually far advanced esophageal or pulmon cinoma, and only palliative medicat tube feeding are indicated

Pneumonitis is a major complic tracheoesophageal fistula

Esophageal Tumors

Leiomyomas and lipomas of the gus are encountered, but the usual t carcinoma We resect cancer of th one-half of the esophagus, as a r esophagogastric anastomosis is used carcinoma of the upper one-half esophagus, the complications, mortali low cure rate have led us to refer p with these lesions for radiation thera

Peptic esophagitis may follow an agogastric anastomosis if a portion acid-bearing portion of the stomach removed, despite the fact that vagot effected by the procedure Regurgita reflux is common

Esophageal Varices with Hemorr

The subject of esophageal varic considered in connection with cirrhosis liver, but a few facts may be reviewe To begin with, the bleeding associate esophageal varices does not always a good correlation with the degree of pr in the portal venous system[61] Too, in ries of 44 patients with bleeding esop varices reported by Wagenknecht a associates,[85] 19 (or 43 1 per cent) s ulceration of the esophageal mucosa lying the varices These ulcerations

felt to be the lesions responsible for the hemorrhage, rather than increased pressure in the portal system, and in one case the evidence pointed to a mechanical break in an esophageal varix. These workers concluded that the acid peptic activity of the gastric juice on the esophageal mucosa was an important factor in the initiation of bleeding in esophageal varices

In a similar study, Chiles and his associates[8] examined the esophagus at necropsy in 91 cases of bleeding esophageal varices In 11 cases no source of hemorrhage could be found In 39 per cent of the remaining 80 cases *ulceration* was present in sufficient degree to have been a primary cause of rupture of the varix.

Regardless of what the cause of the bleeding from the esophageal varices may be, the practical requirement is to control the bleeding and many different approaches to this problem have been made. Among these have been (1) intraesophageal tamponade (2) mediastinal packing (3) transesophageal ligation of the bleeding varices in the emergency, (4) the injection of sclerosing solutions through the esophagoscope (5) esophagogastric resection, (6) splenectomy (7) ligation of the splenic artery (8) omentopexy (9) hepatic artery ligation and (10) (the most effective) portacaval shunt or splenorenal shunt with splenectomy (Fig 75)

Cardiospasm—Achalasia of the Esophagus, Megaesophagus, or Esophageal Dystonia

Cardiospasm is characterized by a variable degree of dilatation of the esophagus associated with an undilated segment adjacent to the stomach which varies in length from one to several centimeters Since there is usually no evidence of stricture or hypertrophy of the muscle in the undilated segment the obstruction is usually considered to be a functional one Achalasia is thought by many to be due to autonomic nervous system dysfunction but this has never been definitely proved Moreover, Cross[14] has stated that while, grossly, certain similarities do exist between megaesophagus and congenital megacolon, the two conditions differ microscopically In megacolon the ganglion cells are missing only in the narrowed segment of the colon and are found in normal numbers in the dilated colon, in megaesophagus the ganglion cells may be missing from all levels of the esophagus

Kay[44] concluded that spasm or hypertrophy of the inferior esophageal constrictor may cause functional stenosis and be an important factor in functional dysphagia, the Plummer Vinson syndrome, esophagospasm, pulsion diverticula of the thoracic esophagus and idiopathic strictures of the terminal esophagus. The etiology of this spasm or hypertrophy was not clear from his studies, but he considered it to be due to spasm similar to that of circular muscle in other smooth muscle sphincters of the body, probably the result of a preponderance of sympathetic control.

Olsen and his associates[69] stressed that particular effort must be made to distinguish cardiospasm from other types of esophageal spasm. In their opinion, diffuse spasm of the esophagus which they considered to be a distinct clinical entity, does not respond to treatment in the same manner as does cardiospasm and the hydrostatic dilator should not be used in cases of nonsphincteric spasm.

Esophageal spasm may, of course be associated with other lesions of the esophagus or gastrointestinal tract such as esophageal diverticula, hiatal hernia, peptic ulceration neoplasms or benign stricture Achalasia may at times simulate disease of the gallbladder

PHYSIOLOGIC ASPECTS OF TREATMENT The appearance of the defect drawn schematically is shown in Figure 107 In the upper diagram the constriction is being treated medically by dilatation for a majority of the earlier cases of esophageal spasm do indeed have great and often lasting relief from dilatation In many patients however dilatation may not be adequate Of 452

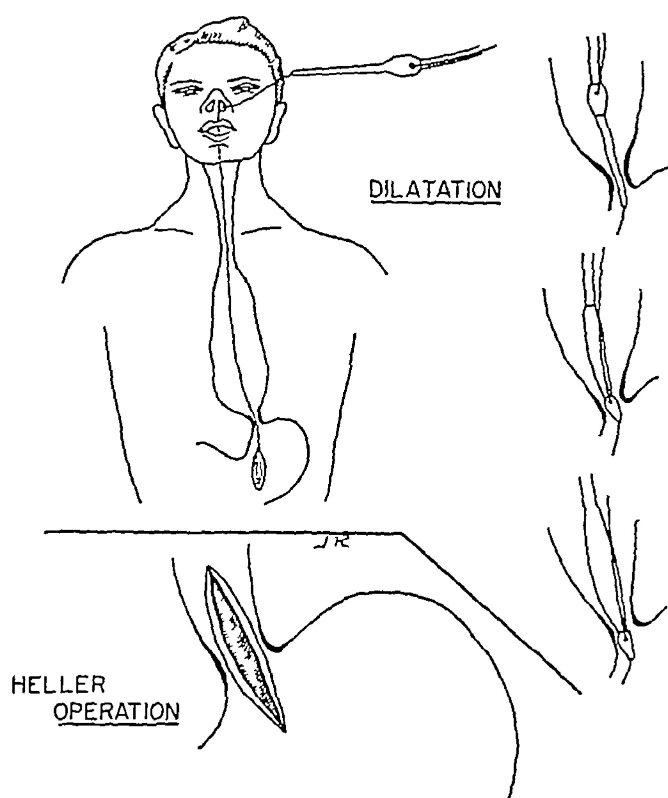


Fig 107 Achalasia is satisfactorily relieved in many patients by esophageal dilatation When operation is required, the Heller procedure, which preserves some degree of sphincteric action, is much superior to resection of the esophagogastric junction with loss of sphincteric effect The disability due to peptic esophagitis that occurs when the sphincter is sacrificed may exceed the disability due to the previous achalasia

patients so treated by Olsen and his associates,[59] 272 (60 2 per cent) were relieved of dysphagia for periods of from 4 to 16 years and were considered to have obtained satisfactory results In the remaining 180 dysphagia recurred in less than 4 years, and the results were considered to be unsatisfactory These workers found that patients who did not respond satisfactorily to the initial course of dilatation were less likely to obtain good results following a second course or from any number of additional courses of treatment In their series, 313 (62 9 per cent) of the 452 patients who could be adequately followed obtained satisfactory and lasting results All in all, these workers concluded that if they had the opportunity to treat all patients as they desired, approximately 80 per cent would obtain satisfactory results from hydrostatic dilatation and the remaining 20 per cent would (presumably) require surgery Only two fatalities occurred in all the dilatations performed, and these were both due to rupture of the esophagus just above the cardia Both these fatalities had occurred before penicillin was generally available, and during the last 11 years covered by the report there had been no deaths Should the esophagus be perforated, it is imperative to operate promptly to provide surgical drainage and, if possible, to close the defect —though some small leaks do close without surgery Antibiotics and blood transfusion are important adjuncts in therapy

PHYSIOLOGIC CONSIDERATIONS IN THE SURGICAL TREATMENT OF CARDIOSPASM Surgery should not be performed until dilatation has been given a reasonable trial (Fig 107), *but operation should not be inordinately delayed*

Numerous procedures have been utilized to produce an adequate lumen between the dilated esophagus and the stomach Few of them have been satisfactory, but among these operations are (1) esophagogastrostomy, as advocated by Heyrovsky, in which a side-to-side anastomosis is performed between the dilated portion of the esophagus and the fundus of the stomach, (2) cardioplasty, advocated by Wendel, which consists of a longitudinal incision extending from the dilated lower esophagus through the constriction and onto the cardiac portion of the stomach, the defect then being closed transversely to enlarge the opening between the lower esophagus and the stomach, (3) a combination of esophagogastrostomy and cardioplasty, as advocated by Grondahl, in which an anastomosis is made between the lower part of the esophagus and the cardiac end of the stomach, after a U-shaped incision has been made through the constricted region of the esophagus and cardia, (4) extramucosal esophagocardiomyotomy, as advocated by Heller, this consists of an incision down to the mucosa, extending from the dilated esophagus through the constricted sphincter region and well down onto

the stomach (similar to the familiar Ramstedt pyloromyotomy performed at the opposite end of the stomach for congenital hypertrophic pyloric stenosis) (5) cardiectomy and resection of the lower part of the esophagus, with esophagogastric anastomosis, (6) resection of not only the lower esophagus but also the major portion of the acid bearing area of the stomach with esophagogastric anastomosis

It is now generally accepted that destruction of the cardiac sphincter mechanism without removing the acid bearing portion of the stomach is all too likely to result in peptic esophagitis and ulceration complications which are apt to nullify any beneficial effect which may have been obtained by the operative procedure Therefore of all the operations listed above only the Heller procedure and the resection of the acid bearing portion of the stomach with re-establishment of continuity are likely to be satisfactory Of these two procedures the Heller operation (Fig 107) certainly is the most innocuous and currently the most successful This is because it preserves the sphincter First proposed by Heller[34] in 1913 the procedure then fell into disuse for many years perhaps because formerly the incision was not carried far enough upward upon the esophagus and downward upon the stomach to span completely the diseased segment We prefer actually to form a gastrotomy lateral to the anticipated abdominal extension of the esophagogastric incision for the myotomy and to cut down upon the finger lying within the esophagus as advocated by others An advantage of the abdominal approach lies in the fact that duodenal stenosis from peptic ulceration may be present and indicated pyloroplasty more easily performed. However we ourselves have been much more satisfied with the thoracic or thoraco abdominal than with the purely abdominal approach If there is chronic scarring around the lower esophagus one can easily perforate the stomach or esophagus at the site of stenosis Meticulous dissection is advisable

As noted above, all operations which sacrifice the cardioesophageal sphincter entail the risk of subsequent *peptic esophagitis* a complication the incidence of which is somewhat reduced by the resection of a liberal portion of stomach A few weeks or months following operation the patient's difficulties may return in a most severe form and are associated with roentgenographic and esophagoscopic evidence of inflammation ulceration and stricture in the lower esophagus The esophagitis results, of course, from the action of the acid pepsin ferment of the gastric juice which in the absence of the cardiac sphincter has free and liberal access to the susceptible esophageal mucosa Indeed, sacrifice of the sphincter may merely convert achalasia to peptic esophagitis the symptoms of which may be more severe and disabling than those of the original disease For example, we know of one patient who following an esophagogastrostomy for esophageal stricture developed peptic esophagitis with eventual erosion into the aorta and fatal hemorrhage into the alimentary tract

Peptic Esophagitis with and without Ulceration[43]

It was predicted by Chevalier Jackson[38] in 1929 that when the time shall have come when every patient with the slightest discomfort or abnormality in swallowing, every patient with regurgitation 'heartburn' or water brash is examined esophagoscopically peptic ulcer of the esophagus will be found less rare than it is now thought to be, though it is probably not a common disease

In 1935, Winkelstein[89] reported on a group of patients with unusual and distinctive esophageal findings The symptoms were those of substernal pain, heartburn sour regurgitation and hyperchlorhydria, symptoms that recalled the clinical picture of peptic ulcer of the esophagus as described by Jackson Esophagoscopy in Winkelstein s cases revealed a diffuse inflammation of the esophagus without a definite ulcer The

symptoms, due to esophagitis, were relieved by antacid and other conservative measures usually employed for the treatment of peptic ulcer

Peptic esophagitis is frequently associated with hiatal hernia. Allison[1] reported on 204 patients with diaphragmatic hiatal hernia and pointed out the significance of paraesophageal hiatal hernia in the occurrence of reflux esophagitis Moreover, peptic esophagitis, with or without ulceration, is frequently associated with duodenal ulceration, both lesions being in part a result of the digestive effect of the gastric acid-pepsin factor

The final stage of chronic peptic esophagitis is likely to be the formation of a benign fibrous stricture of the lower esophagus Although most strictures can be controlled by esophageal dilatation and other conservative measures, some cases require resection of the lower esophagus (which incidentally effects vagotomy) and proximal stomach, with esophagogastrostomy Of 20 cases with peptic esophagitis reported by Winkelstein and his associates,[90] 15 were associated with simultaneous duodenal ulcer and 2 with gastric ulcer

To summarize, peptic esophagitis is a common disease of this organ An important consideration in doing a surgical procedure for stricture and/or ulceration of the esophagus is to be certain that there is not also a stenosing ulcer of the duodenum which, if not dealt with simultaneously, may cause gastric retention (especially following vagotomy) and negate the beneficial results which might have resulted from the operation upon the cardia Moreover, a considerable amount of the acid-bearing portion of the stomach must be removed In reviewing 65 patients who had resection of the cardiac sphincter mechanism with esophagogastrostomy, Kirklin and his associates[60] found that 29 subsequently had positive signs and 12 had presumptive signs of peptic esophagitis and stricture formation To minimize such complications, where resection of the sphincter cannot be avoided, the acid-pepsin factor must be reduced

Spontaneous Rupture of the Esophagus

While spontaneous perforation of the "normal" esophagus is relatively rare, a considerable number of cases have now been reported, and almost all surgical cente have had experience with this condition Tl case first reported was in 1724 by Herma Boerhaave[5] of Holland

Characteristically, the rupture occu when a patient, who often has been drinkin heavily, vomits violently and raises tl pressure in the esophagus abruptly (Fi 108) The lower esophagus tears in a long tudinal direction (usually on the left) an the patient is seized with severe pain i the lower substernal region, the epigastrium and/or the left lower thoracic portion c the spine A shocklike state ensues, wit cold and clammy skin and a rapid puls Roentgen examination may reveal air an fluid in the mediastinum or in the lef pleural space

Mackler[52] studied the posible etiolog and mechanism of this condition in cadaver and reported three clinical cases His find ings appeared to confirm the general im pression that spontaneous rupture of th esophagus is an accident which may follow a sudden rise in intra-abdominal pressure Vomiting is the usual cause but other act which have resulted in rupture are strain ing at defecation, lifting a heavy weight, a convulsive seizure of grand mal epileps, and the labor of childbirth The triad of vomiting, low thoracic pain, and emphysema of the neck is diagnostic and constitutes sufficient evidence to warrant a left thoracotomy If the physician even considers the possibility of esophageal rupture, the diagnosis will usually be made Mackler found that the evidence supported the conclusion that rupture may occur in a previously normal, healthy esophagus as a result of increased intraesophageal pressure, transmitted from the stomach The rupture usu-

formly occurred at the lower extremity of the esophagus. That this was, in fact, the weakest part of the organ was confirmed by experimentally inflating and bursting the esophagi of 65 fresh human cadavers. The site and configuration of the resulting rupture *duplicated exactly the clinical lesions* found.

Spontaneous rupture of the esophagus was uniformly fatal before the adoption of left thoracotomy with suture of the rent and adequate drainage. Antibiotics are given in large doses along with adequate supportive therapy in the form of blood transfusions and other measures.

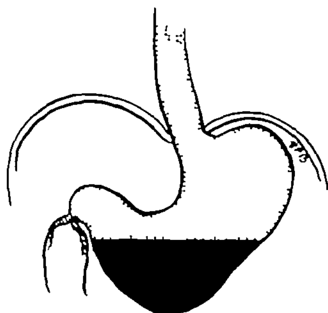


Fig. 108. Mechanism of esophageal rupture in severe vomiting. Diagrammatic representation of the mechanism of vomiting. (Top.) Inhibition of tone and flaccid relation of the cardiac pouch and sphincter of the stomach. *Bottom.* Sharp contraction of the diaphragm and abdominal muscles with resultant compression of the stomach and forcible ejection of its contents into the esophagus. (From MACKLER, S. A. Spontaneous rupture of the esophagus. Surg., Gynec. & Obst., *95: 345, 1952.*)

The longitudinal tear almost always occurs in the left side of the organ just above the diaphragm (Fig. 106). The diagnosis is made on the basis of the history of vomiting (often in an alcoholic), severe sudden pain beneath the sternum, and roentgen evidence of mediastinal emphysema or effusion. Shock commonly develops.

Diaphragmatic Hernia

TYPES. A diaphragmatic hernia is a protrusion of certain or most of the abdominal viscera into one or the other hemithorax *through a normal or an abnormal opening* in the diaphragm. It may result from imperfect development of the diaphragm during embryonic life, anatomic weakness, traumatic injuries, or inflammatory processes (Fig. 109). The majority are actually false hernias in that they are not enclosed in a sac of *peritoneum*. Diaphragmatic hernias occur more often on the left, and this is probably due to the protective position of the liver on the right.

Herniation through the aortic and vena caval apertures must be very rare. The retrosternal hernia traversing the foramen of Morgagni is occasionally encountered as a mass presenting in the anterior mediastinum; in this position it is often confused with mediastinal tumors such as pericardial cyst, dermoid, lipoma, and the like.

Traumatic diaphragmatic hernias may occur in any anatomic location. The symptoms are chiefly respiratory or gastrointestinal, resulting from pulmonary compression or alimentary obstruction; moreover, symptoms may be absent, mild, or severe. The defect may remain innocuous for years only to end in disaster. We recall a patient, stabbed in the left chest, who initially was

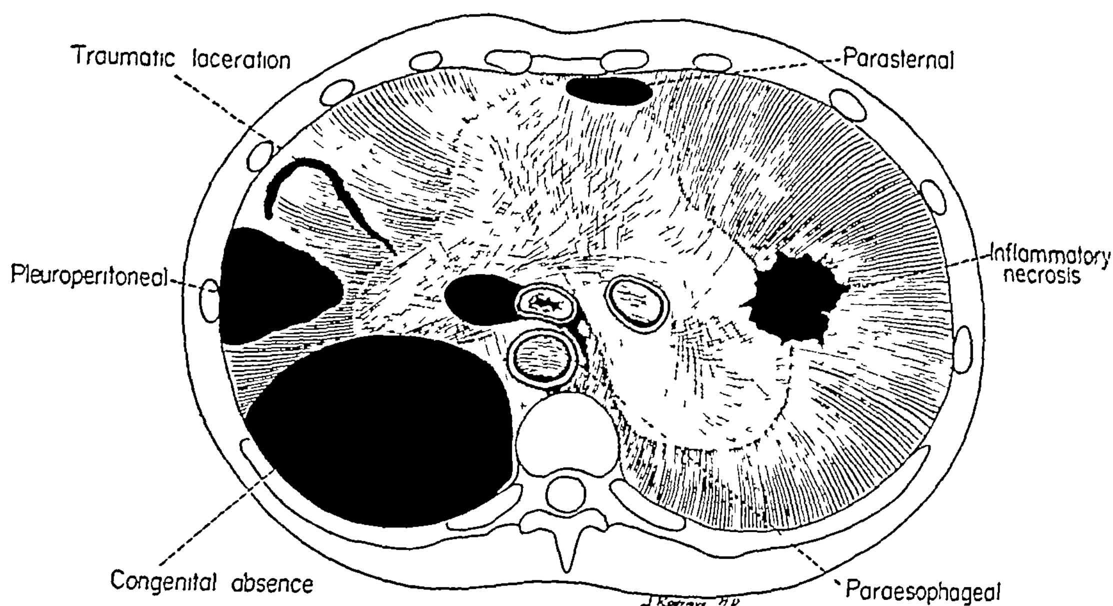


Fig 109 Diaphragmatic hernias in adults are usually more satisfactorily repaired from above, in our experience

managed conservatively. However, empyema developed in the residual hemothorax This was drained by rib resection and he recovered uneventfully The possibility of diaphragmatic injury was considered at the time, but the matter was not further pursued in view of the fact that he had no suggestive symptoms Six years later, while hoisting a large container of garbage onto a garbage truck, he was stricken with sudden, excruciating pain in the lower left chest, followed by cramping abdominal pain He delayed coming to the hospital and there was further delay after admission since, while the possibility of intestinal obstruction was thought of, it did not sufficiently impress the resident to prompt immediate exploration The following day the abdomen was explored A left diaphragmatic hernia was found and the left hemithorax contained several feet of gangrenous jejunum The patient died

Traumatic hernias should be repaired

DIAPHRAGMATIC DEFECTS FROM INFECTIONS Perforations of diaphragm may occur from subdiaphragmatic collections of purulent material, and especially prone to penetrate this barrier are amebic parasites and the fungus *Actinomyces bovis* Either of these organisms may result in a bronchopleural fistula, and the offending agents may identified in the sputum

DIAPHRAGMATIC HERNIA IN THE NEWBOR[N] The complete absence of a diaphragmat[ic] leaf (actually a misnomer, since caref[ul] search will usually disclose at least a rim) is rare but does occur. The most common an[d] important hernia in the newborn is that ex[]tending through the pleuroperitoneal fora[]men (Bochdalek), usually on the left Th[e] respiratory distress, cyanosis, perhaps vom[]iting, and the ausculatory findings of bowe[l] sounds in the chest, along with collatera[l] roentgen evidence, establish the diagnosis

Severe symptoms may necessitate im[]mediate operation to diminish cardiopul[]monary embarrassment, and reduction o[f] the hernia is readily effected through a[n] abdominal incision On the other hand, occasionally the hernia may remain asymptomatic throughout life We recall a patient in his thirties, a member of a "tuberculous family," who was admitted for a tuberculosis work-up after a routine county health unit film had revealed "pleural thickening and opacification" of the right hemithorax Further studies and eventual operation disclosed complete displacement of the liver into the right chest, with an atrophic right lung compressed into the apex After con-

siderable effort it was possible to return the liver to the abdomen and close the defect Possibly this hernia would have remained quiescent throughout life, but in general congenital hernias should be repaired when discovered to avoid emergency operation for serious complications

ESOPHAGEAL HIATAL HERNIA (THE COMMON "DIAPHRAGMATIC HERNIA" OF THE ADULT) The hiatal hernia results when pressure within the abdomen forces the fundus of the stomach and adjacent peritoneum through the diaphragm. The esophagogastric junction may or may not remain fixed in the normal position. The herniation occurs because the hiatal opening is too large but there is considerable variation in the size of this space normally This hernia occurs more frequently in women whereas traumatic hernias are far more common in men

Finally there is the *congenitally short esophagus*, in which situation the stomach extends upward through the hiatal opening.

SYMPTOMATOLOGY OF HIATAL HERNIAS (FIG 110) The symptomatology of hiatal hernias varies greatly Complete asymptomatic hernias are often discovered incidentally when patients are being examined for other conditions but other individuals may have incapacitating distress

Pain is the symptom which usually brings the patient to operation Sweet[8] analyzed 130 cases treated surgically and found that the principal indications for surgery were pain and dyspeptic disturbances This pain was felt primarily in front sometimes in the upper abdomen and sometimes over the lower thoracic area When felt in the abdominal region it was usually in the mid epigastric area. Twelve patients noted pain in the left upper quadrant and five others spoke of it as being in the right upper quadrant. Gallbladder disease coronary occlusion and angina were among the conditions which frequently had to be ruled out One individual felt pain only in the mid-dorsal region of the back. Although with one exception the initial reference of pain was to the front of either the abdomen or the tho

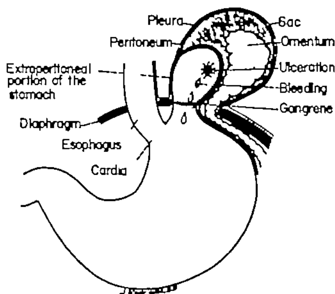


Fig 110 It is often difficult to determine whether a patient's symptoms are actually due to the hiatal hernia Some complications of this lesion are shown

rax 20 patients experienced a sense of radiation of the pain to the back, 14 to the neck, and 18 to the shoulders arms, or wrists Relief of pain by a change in posture from the supine to the erect position was experienced by 39 patients, while in 3 the supine position was the more comfortable one

A particular problem in the management of some patients was that at times it was impossible to be certain as to the rôle played by the hernia in causing the pain. In this group Sweet felt that useful diagnostic information was obtained by inflating a balloon at various levels of the esophagus Moreover such studies were found by Jones and Chapman[42] to be of much value in excluding from surgical consideration the patient with both coronary disease and a hiatal hernia In such a patient failure to reproduce the pain by distending the balloon should cause the physician to concentrate on the treatment of the cardiac condition alone unless the hernia is thought to represent a so-called 'trigger point' from which stimuli might arise that would bring about anginal attacks in a reflex manner However hiatal hernias may themselves at times produce electro-

cardiographic effects similar to those which may be associated with attacks of gallbladder colic

Another characteristic of hiatal hernia pain in some subjects is that the ingestion of only a few mouthfuls of a meal may precipitate marked distress This may be relieved by arising and walking around for a few moments, after which the meal can be continued in comfort

Instead of pain, the patient with hiatal hernia may merely have a feeling of fullness in the upper gastric or lower thoracic region, eructations of "gas", or a feeling of burning or oppression beneath the sternum These symptoms are referred to the same anatomic sites as is actual pain when present

Fifty patients in Sweet's series had the above symptoms Nausea was not a prominent symptom and, although occasional vomiting was experienced by 26 patients, in the majority of these it was self-induced in an effort to relieve a feeling of fullness or distress of a dyspeptic nature When severe vomiting was present (19 patients) it was indicative of some obstruction, usually occurring when the hernia was exceptionally large with partial volvulus of the stomach Complete obstruction requiring emergency surgery was experienced in only 2 patients In 1 of these the stomach was incarcerated, with early ischemic changes from an occluded blood supply

Bleeding was observed in 40 patients (30 per cent), and this bleeding was considered to come from the herniated portion of the stomach In 29 the bleeding was episodic, with sudden relatively massive hemorrhages usually manifested by the passage of tarry stools, occasionally by hematemesis In 11 instances blood loss was slight but continuous, resulting in hypochromic anemia

Narrowing or compression of the esophagogastric junction may interfere with normal passage of food into the stomach Resulting dysphagia and regurgitation are frequently made worse by exertion or by change of position Compression of the herniated portion of the stomach by the diaphragm may prevent normal venous drainage and thereby may produce marked hyperemia of the gastric mucosa This congested mucosa is often traumatized and superficial erosions or ulcerations develop The slow but persistent loss of blood may lead to the anemia mentioned above, but it is to be remembered that in some cases the alimentary bleeding may arise in a concomitant duodenal ulcer.

SOME ADDITIONAL CONSIDERATIONS IN REPAIR OF DIAPHRAGMATIC HERNIAS Certain of the physiologic implications are implicit in the previous discussion of various types of hernias and their symptoms and pathology For example, it may be quite difficult to return all of the abdominal organs to the peritoneal cavity in an infant in whom most or a large part of the abdominal viscera are found in the thorax, and various types of alimentary and cardiorespiratory dysfunction may occur Recurrence of diaphragmatic hernia is not a rare complication, and occasionally symptoms persist following the repair It is especially important to exclude other intra-abdominal pathology before repairing the hernia, since the symptoms may be due to malignancy

Physiologic Basis of Gastric Surgery

Modern gastric surgery is based upon a knowledge of gastric secretory physiology This has been developed over the past two centuries since Réamur (1752) isolated the gastric juice of birds and demonstrated its solvent effect upon foods[68] These observations were confirmed and extended by others during the succeeding decades, but the next truly major advance, particularly as it affected human physiology, was Beaumont's classic study of the gastric fistula of Alexis St Martin in 1833[2] His observations resulted in the formulation of the broad concepts of the processes of gastric secretion as they are known today The importance of the cephalic phase was demonstrated by Pavlov[61] in 1910, when he established the concept of the conditioned reflex

ANATOMY The regional anatomy of the stomach is shown in Figure 111 The stomach may be thought of as consisting of the cardia body and pylorus but it is helpful to subdivide the cardiac portion into the fundus and the region adjacent to the esophageal opening and to subdivide the lower stomach (pyloric portion') into the pyloric antrum the pyloric canal and the muscular pylorus itself

Physiology of Gastric Secretion

The main *gastric glands* are situated in the fundus body, and part of the pyloric region of the stomach These glands are lined by two types of cells, the chief or peptic cells which secrete pepsin (from an inactive precursor, pepsinogen) and the parietal cells which secrete hydrochloric acid The surface lining of the stomach consists of columnar epithelial cells between which lie many mucus secreting goblet cells There are also many goblet cells in the necks of the glands. The pyloric glands secrete an alkaline fluid which is rich in mucus and has considerable neutralizing power but is poor in chloride and digestive enzymes [94]

The gastric juice contains the strongly acid solution from the parietal cells The strong hydrochloric acid is essential for peptic digestion and it has some antiseptic action. The chief cells as noted secrete pepsin which in the presence of hydrochloric acid breaks down proteins to peptones It is possible that the chief cells also secrete rennin and lipase Rennin curdles milk by acting on its caseinogen which in the presence of ionic calcium precipitates an insoluble calcium caseinate

The three phases of gastric secretion may be referred to as the nervous or *cephalic* the *gastric* or humoral and the *intestinal* phases[18, 20-23] (Fig 112) These terms refer to the fact that secretion by the gastric glands in the body and fundus of the stomach may be stimulated by impulses in the vagus nerve aroused reflexly by the sight odor or taste of food and certain emotions (cephalic phase) and by the presence of

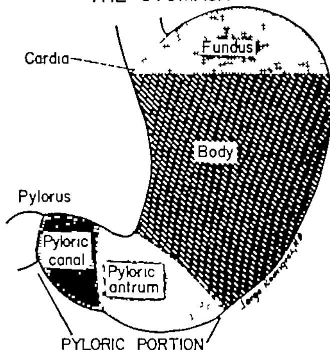


Fig 111 The antral secretion is alkaline and here gastrin is formed The acid-secreting cells are in the body and fundus. The cardiac sphincter is vital to the protection of the esophagus from erosion by the acid-pepsin factor

food within the stomach (gastric phase) or intestine (intestinal phase) Dragstedt and his associates[20] investigated the relative importance of the three phases and found that in normal dogs the nervous phase of secretion accounted for approximately 45 per cent of the gastric juice secreted in a 24-hour period the gastric phase for about 45 per cent, and the intestinal phase 10 per cent or less However, these were only estimates since there appeared to be a definite interrelationship between at least the nervous and gastric phases of secretion. For example, the removal of the nervous phase of secretion by complete vagotomy likewise materially reduced the gastric phase of secretion and the elimination of the gastric phase of secretion in turn reduced the effectiveness of the nervous phase *The gastric phase of secretion was found to be mediated exclusively by the mucous membrane of the antrum of the stomach* which functions as an endocrine organ for the manufacture of the gastric secretory stimulant *gastrin* the antral mucosa is stimulated to form gastrin when food comes

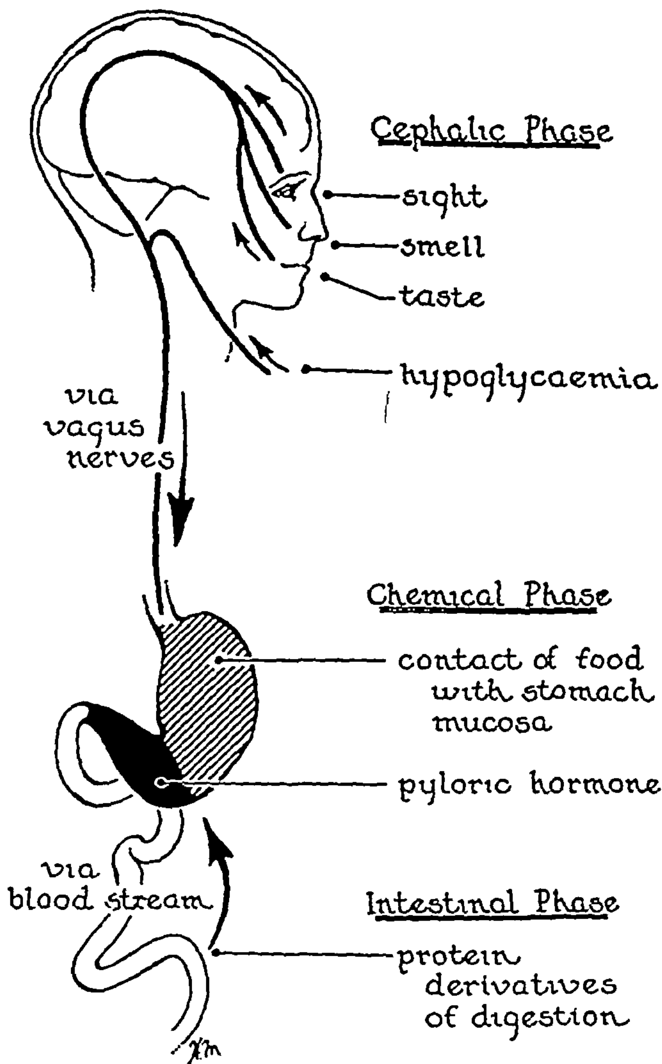


Fig 112 Mechanism of the stimulation of gastric juice secretion The cephalic phase and the gastric (chemical) phase are the most important The cephalic phase is abolished by vagotomy, the gastric phase is reduced by subtotal gastrectomy (WEBSTER, D R In *Textbook of Surgery*, Ed 2, edited by H F Moseley St Louis, C V Mosby Company, 1955)

into contact with it or when the antrum is moderately distended Removal of the antrum in Pavlov pouch dogs, or transplantation of the antrum so that it did not come into contact with food, abolished the gastric phase of secretion [93] When both the nervous and the gastric phases of secretion were eliminated, as by complete vagotomy and removal of the antrum, the secretion of gastric juice by the body and fundus of the stomach was reduced to a negligible amount, indicating that the intestinal phase of secretion is relatively unimportant

As stated, the antrum of the stomach was found to be the sole source of the gastric secretory excitant, *gastrin*, and to function as an endocrine organ, transplantation of the antrum of the stomach into the colon caused a greater secretion of gastric juice than was produced when the antrum was in its normal location This secretory stimulus continued even though the regional blood supply to the antrum was divided, allowing it to be nourished by newly formed blood vessels from the colon In the absence of other factors, the development of pressure within the isolated colon containing the antrum transplant as a result of peristalsis was a profound stimulus for antral function This finding suggests a possible explanation for the increase in gastric secretion which accompanies pyloric stenosis in man, namely, that unrelieved gastric distention affords a continuous stimulus for antral elaboration of gastrin

TESTS FOR GASTRIC ACID SECRETION Tests for gastric secretory activity are performed in several ways

Fractional test meal The usual test of gastric secretion is performed in the following manner A nasogastric tube is introduced into the stomach before breakfast, with no food having been eaten since the previous evening The resting contents of the stomach are aspirated and used for the first specimen The stomach is then irrigated with distilled water and this is withdrawn Next, approximately a pint of gruel is swallowed and 10 ml of gastric contents are aspirated at intervals of 15 minutes until the stomach is empty Each sample is titrated with sodium hydroxide to determine the amount of free hydrochloric acid and the total acidity A sample curve is shown in Figure 113 The resting specimen amounts to an average of 30 ml of fluid, and free hydrochloric acid can usually be demonstrated The ingestion of the gruel usually lowers the free acid almost to zero level This is due to dilution of the gastric juice, its neutralization by swallowed saliva, and its combination with organic substances in the test meal The acidity of the gastric contents usually then slowly rises, and after 1½ hours reaches perhap

0 1 per cent hydrochloric acid, equivalent to 30 ml of 0 1 N NaOH per 100 ml of gastric contents The presence of the food and water in the stomach has thus called forth a second flow of gastric juice, the gastric phase, and as this secretion is added to the stomach contents the acidity slowly rises[24]

As might be suspected, the response to the test meal shows considerable variation in different subjects—depending upon the quantity of acid secreted in response to the meal, the rate at which the test meal leaves the stomach, the amount of intestinal contents regurgitated into the stomach to neutralize partially the gastric acid and other factors Actually the fractional test meal has fallen into considerable disrepute, and it is not nearly so widely used as formerly

The histamine test of gastric secretion[24] Histamine is a powerful stimulant to the secretion of gastric juice and for a time it was considered to be identical with gastrin. However it has now been established that gastrin and histamine are not identical Histamine acts mainly on the parietal cells and causes an increased volume of highly acid gastric juice with a low pepsin content Incidentally this is in contrast to the effect of the administration of insulin, which considerably increases peptic activity as well The insulin stimulus is mediated over the vagus nerves

The *histamine test* is performed as follows First the resting gastric contents are aspirated through the nasogastric tube and the stomach washed out Then 0 5 mg. of histamine is injected subcutaneously The gastric contents are aspirated intermittently and the volume and acidity of each 10 minute sample are determined. On the average the highest level of acidity obtained is 102 ml of 0 1 N hydrochloric acid. The volume of 0 1 N acid secreted in 1 hour is on the average 182 ml The volume of juice in 1 hour is approximately 200 ml.

The histamine stimulus tests almost specifically the functional state of the parietal cells and in this respect it resembles the action of gastrin.

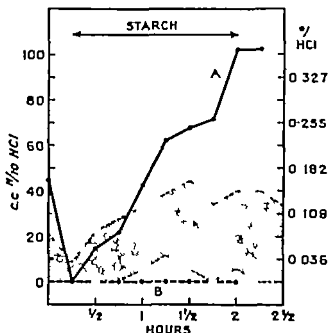


Fig 113 Fractional test meal (Bennett and Ryle) Ordinate cc of N/10 HCl (*left*) or gm of HCl (*right*) in 100 cc of aspirated gastric contents Shaded area represents the limits of free HCl in 80 per cent of healthy males after a test meal. A = "climbing" type of curve B = achylia gastrica The emptying time of stomach is measured by the disappearance of starch (in this figure after 2 hours)

The gastric analysis still affords the surgeon valuable information If the patient with pyloric obstruction has a high level of gastric acidity the resection of a liberal amount of stomach may be indicated If there is little or no acidity a simple gastroenterostomy may be judicious in an elderly poor risk patient (From WRIGHT S *Applied Physiology* Ed 9 London Oxford University Press 1955)

Insulin test of gastric function[25] The injection of insulin (20 units regular) is followed in man by a marked secretion of gastric juice resembling that produced by vagal stimulation in that it is rich in both hydrochloric acid and pepsin The response begins after a latent period of about 40 minutes, and its onset coincides with a considerable fall in the blood sugar to levels of perhaps 70 mg per 100 ml, accompanied by the usual prodromal signs of hypoglycemia such as dizziness or drowsiness The insulin does not act directly upon the gastric secretory mechanisms but produces its effects solely by virtue of resulting hypoglycemia It has been shown in cross-circulation experiments

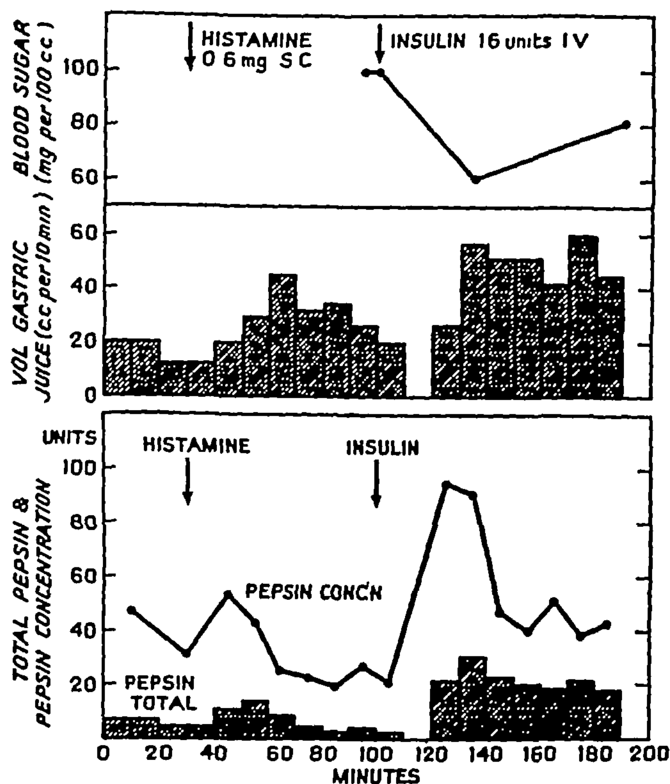


Fig 114 Comparison of action of histamine and insulin on gastric secretion in man Histamine stimulates the gastric secretory cells directly Insulin stimulates indirectly by lowering the blood sugar, this causes the hypothalamus to initiate vagal impulses that increase gastric secretion Therefore, the effect of insulin on gastric secretion is abolished by vagotomy, and the presence or absence of an insulin effect upon gastric secretion is used as evidence of the completeness of vagotomy (From WRIGHT, S *Applied Physiology*, Ed 9 London, Oxford University Press, 1955)

that the hypoglycemia acts on the central nervous system and causes increased activity over the vagal secretory supply to the stomach (There is evidence that adrenocortical hormones may also play a part in this response to hypoglycemia) The gastric response to hypoglycemia is virtually abolished by double vagotomy or by suitably large doses of atropine, and this is of course the basis for the commonly used insulin test to determine the completeness of vagotomy

A combined insulin-histamine test stimulates the maximum secretory capacity of the gastric mucosa The two are compared in Figure 114

QUANTITATIVE METHODS FOR THE STUDY OF THE SECRETION OF GASTRIC JUICE Dragstedt and his associates[21] have emphasized that quantitative methods of studying gastric secretion are usually necessary to demonstrate certain types of deranged function, and for this reason should replace determinations of the free acid concentration and fractional samples of the gastric content, the latter give little or no information concerning the actual amount of hydrochloric acid manufactured by the stomach throughout the day and night If quantitative methods of collection are applied, data obtained from gastric analysis are of definite value in the diagnosis of duodenal ulcer and, more especially, in forecasting the success of certain medical measures of management and the probable necessity for eventual surgic therapy These workers reported two p tients who secreted 330 and 337 mEq hydrochloric acid in the 12-hour night p riod, as compared with the normal avera of 18 mEq It was considered unlikely th this large secretion of acid could be co trolled satisfactorily by any type of medic management the patients could long tole ate, and that surgical measures to reduc the secretion would have to be used

Dragstedt and his associates place th nasogastric tube in the lower portion of th stomach under fluoroscopic control an maintain constant suction from 9 o'clock i the evening until 9 o'clock the followin morning During this 12-hour period the pa tient is shielded from the sight, odor an taste of foods and, since all food has bee removed from the stomach by a preliminar gastric lavage as well as by the period o fasting, the usual physiologic stimuli fo gastric secretion are absent Some portio of the gastric secretion inevitably escape through the pylorus and thus the collection is often incomplete In fact, when hypermotility of the stomach is present, as occurs during the insulin test, the amount of gastric secretion recovered may actually be relatively small as compared with the total amount secreted and may render the determination of little value in such patients Even so, the indwelling tube may be utilized to measure in a more quantitative fashion the secretory response of the stomach to

such stimuli as histamine and insulin hypoglycemia, such tests being performed while the nasogastric tube is still in place following collection of the night secretion. One milligram of histamine acid phosphate may be given subcutaneously and the gastric secretion collected by continuous aspiration for a period of 60 minutes. A similar technic may be employed to determine the gastric secretory response to insulin hypoglycemia, in which case one injects 20 units of regular insulin and makes a 2 hour collection of gastric secretion; determinations of the blood sugar levels are done to ascertain the degree of hypoglycemia produced. Here too a variable volume of the secretion may leave the stomach via the pylorus and be lost to suction.

THE TUBELESS METHOD FOR DETERMINATION OF GASTRIC ACIDITY. In an effort to improve methods of gastric analysis Shay, Ostrove, and Siplet[76] re-examined the possibilities for such measurements. They found that the inadequacy of the usual gastric analysis was perhaps even greater if the method was used to evaluate the effect of subtotal gastrectomy on the secretion of the remaining gastric pouch. From their studies the determination of hydrogen ion concentration (pH) of the gastric contents was found to be the most precise method for establishing the true status of gastric acidity when no titratable free acid was present. It was considered vital for the ulcer patient who had had a subtotal gastric resection to develop relative anacidity in the remaining gastric pouch if he was to be safeguarded against the development of new ulcers. It was recommended that the gastric secretion in such patients be measured shortly following operation and at frequent intervals thereafter until a satisfactory gastric anacidity was established. They noted that the lower level of gastric secretion might not be realized for from 4 to 6 months following the subtotal gastric resection and it was advised that all patients be continued on a strict medical regime until the acid secretion of the remaining pouch of the stomach had stabilized at the lowest level which it could attain. The explanation for the delay in the fall of the acidity in the remaining gastric remnant was not clear.

Shay and his associates re-evaluated the tubeless method reported by Segal, Miller, and Morton[76] who employed this technic as a test for determining the presence or absence of free hydrochloric acid in the stomach without subjecting the patient to intubation. The principle of the test lies in the use of a cation exchange resin to which is attached a special indicator cation that can be readily identified when it is released from the compound by an ion exchange reaction. Clinical trials were based on administration of a quininium exchange indicator compound prepared by subjecting an acid-conditioned cation exchange resin to a solution of quinine hydrochloride. By this treatment quinine replaces the hydrogen cations of the carboxylic acid groups present in the resin. If free hydrochloric acid is present in the stomach, the quinine will be replaced by hydrogen ions and the liberated quinine will be absorbed into the blood stream and can soon be detected in the urine. The greater the amount of acid in the stomach the greater the urinary excretion of quinine.

Small amounts of quininium cations may be displaced by the cations present in the secretions of the small intestine, but these quininium cations can be differentiated from those displaced by the hydrogen ions in gastric juice by the time of their appearance and the amount of quininium cations in the urine. It has been suggested that the simplicity of the tubeless test of gastric acidity may render it useful as a screening measure for the selection of achlorhydric subjects in the gastric cancer age group for further investigative studies.

Unfortunately, Shay and his associates[76] concluded that the tubeless method for determining the presence of free hydrochloric acid in the remaining pouch following gastric resection was not reliable, probably as a result of the fact that the rapid emptying of the remaining pouch allowed insufficient time for the quinine to be displaced by hy-

drogen The determination of the pH of gastric contents during an adequate fractional gastric analysis appeared to be the best method for studying gastric acidity after subtotal gastric resection

Abnormal Gastric Acid Values

An elevated secretion of hydrochloric acid is a predisposing factor in duodenal ulceration It is frequently associated with emotional stress, but certain nonfunctioning tumors of the islets of Langerhans have recently been reported to be associated with increased gastric acid production, the so-called ulcerogenic tumors of the pancreas[95]

Gastric acid is decreased or absent in patients with pernicious anemia, is usually absent in the presence of gastric cancer, and normally tends to decline with advancing age It may also be subnormal in diabetes mellitus, hyperthyroidism, and Addison's disease

Secretion of Pepsin and Peptic Activity in the Stomach

The administration of histamine does not increase pepsin secretion by the chief cells of the stomach, but the administration of insulin does induce an increase in the secretion of pepsin by virtue of the effect of the hypoglycemia on the central nervous system to stimulate vagal activity Ferguson[27] found that the pepsin output in dogs was decreased by over 50 per cent after vagotomy The humoral phase of gastric pepsin secretion appeared to be of little importance Janowitz and Hollander[39] examined gastric pepsin content and found a high degree of positive correlation between the basal secretion of pepsin and of acid, suggesting that in the basal state the chief and the parietal cells were responding to some common influence, possibly of vagal origin The basal secretion of pepsin and acid was measured for periods of 3 hours in 61 individuals who presented wide variations in clinical diagnosis and in secretory activity Twenty-one duodenal ulcer patients secreted, on the average, 3 times as much pepsin per hour as did the 26 individuals of the control group without gastrointestinal lesions The patients with duodenal ulcer also secreted more acid in the basal state than did the controls A small group of 4 gastric ulcer patients and 5 gastric carcinoma patients fell within the normal range of secretory behavior

Blood pepsin levels and the *urinary excretion* of this enzyme have also been studied In brief, it has been shown that the pepsinogen or propepsin is absorbed into the circulation and excreted in the urine as uropepsin This excretion may be increased in peptic ulcer patients, especially during exacerbations of ulcer activity; similarly, blood pepsin levels may be elevated in these subjects Nevertheless, thus far our own experience with blood pepsin and uropepsin measurements has not led us to believe that the correlation between duodenal ulcer and an increased pepsin secretion is nearly so consistent as between duodenal ulcer and increased acid secretion Moreover, there are wide variations in the blood pepsin levels obtained among "normal" patients and in the same patient at different times[54]

Effect of Foodstuffs on Gastric Secretion

Meat and protein extracts are strong stimulants of gastric secretion, while carbohydrates have little effect Fats promote a secretion of gastric juice while in the stomach, but after passing into the duodenum they stimulate the formation of a substance which causes marked inhibition of gastric secretion This substance has been termed "enterogastrone"

Gastric Motility

The stomach exhibits both tone and peristalsis, and its motility appears to have an important relationship to the pain associated with peptic ulcer Gastrointestinal motor activity in human beings may be studied with the aid of inlying balloons

Peptic Ulcer

Etiology and Pathogenesis

1 GASTRIC SECRETION AND ITS RÔLE IN ULCER FORMATION The basic mechanism which

finally results in actual ulceration of the stomach or duodenum is not yet known, but there is general agreement that certain predisposing factors are quite important (Table 13) The *most significant of these are those* which influence the amount of hydrochloric acid and, to a lesser extent, of pepsin secreted by the stomach The dictum "no acid no ulcer" still remains a valid practical summary of the ulcer problem, from the surgical point of view The chief objective of both medical and surgical forms of treatment is to reduce the acidity of the stomach (and the upper duodenum) to below the optimum level for the digestive action of pepsin Active duodenal ulcers in the presence of gastric achlorhydria are rare

While the presence of an increased gastric acidity is important in the formation of duodenal ulcer it need not follow that the increased acidity in itself is responsible for the ulcer many individuals exhibit hyperacidity without ulcer Moreover, the duodenal ulcer can heal and recur spontaneously with no significant variation in the degree or quantity of acid present. Clearly, then hyperacidity *and hypersecretion alone* are not responsible for the development of ulcer and there must therefore be other factors which render the mucosa susceptible to the digestive action of acid pepsin These other factors may, moreover be exceedingly important. For example the mucus secreted provides a protective influence in both the stomach and duodenum and it may play a prominent rôle in *the local defense mechanism* against ulceration

1 THE PSYCHOGENIC FACTOR. The emotional aspect is considered separately from gastric secretion *per se* chiefly for emphasis The observations of various persons regarding emotional turmoil have shown that there is hypersecretion of hydrochloric acid and pepsin during anger and resentment, while fear or insecurity are likely to have an *opposite* effect. The frequency with which striving and emotional crises are associated with the development of an active duodenal ulcer, or the reactivation of an established ulcer is too great to be merely coincidental Of course, such psychogenic stress acts largely through vagal stimulation of gastric secretion, but endocrine and other as yet undiscovered effects of psychic stress may be operative (Fig 115)

2 CONSTITUTIONAL FACTORS *It has always* been a matter of interest that one person

TABLE 13 ETIOLOGIC FACTORS IN SOME PEPTIC ULCERS

1 Emotional stress—vagal mediation?
2 Severe trauma such as a burn (Curling's ulcer) —adrenocortical mediation?
3 Brain (hypothalamic) injury—Cushing's ulcer
4 Cushing's disease (adrenocortical hyperplasia or adenoma)
5 Parathyroid adenoma
6 Pheochromocytoma
7 Ulcerogenic tumor of pancreas
8 Polycythemia

SCHEMA FOR THE ACTION OF STRESS ON GASTRIC SECRETION

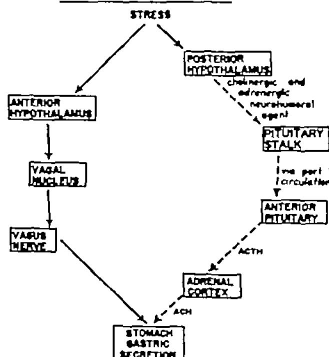


Fig 115 A diagrammatic representation of two types of hypothalamic stress stimulation of gastric secretion (Cushing's type on the reader's left and Curling's type to the right This schema indicates the alternate pathways for the mediation of impulses that result in stress ulcers (From Shay H Stress and gastric secretion. Gastroenterology **26**: 316 1954 as modified by HARKINS H N In *Surgery—Principles and Practice* edited by J G Allen, H. N Harkins C A Moyer and J E Rhoads Philadelphia, J B Lippincott Company 1957)

may develop an ulcer under a particular type of stress, whereas another person under the same stress does not develop ulcer Certain constitutional types of individuals have throughout literature been looked upon as those likely to predispose to the development of an ulcer, and persons with these personality traits and body build are referred to as representing the "ulcer type"

It is this predisposition to ulcer formation, by virtue of personality make-up, that constitutes the basic difficulty in most patients with ulcer—for life stress and the patient's reaction to it can be modified but not abolished, surgery or no surgery *Duodenal ulcer is a constitutional disease*

THE MOTILITY FACTOR It has been suggested that hypermotility of the stomach and duodenum may act to interfere with local blood supply, resulting in devitalization of tissue and subsequent ulceration While gastric tone may be of importance in the pathogenesis of peptic ulcer, one doubts that it is a major factor in this connection

ISCHEMIA It is not possible readily to produce typical peptic ulcers by interference with either the arterial or the venous blood supply alone Yet, there are certain types of ischemia, such as that in polycythemia, which may result in the production of an ulcer Therefore, lowered tissue resistance resulting from ischemia may be important in the production of some ulcers

ENDOCRINE INFLUENCES WITH SPECIAL REFERENCE TO ACTH AND CORTISONE Various types of endocrine dysfunction may predispose to the development of peptic ulcer, and patients with Cushing's disease may exhibit peptic ulceration Furthermore, in severe stress reactions, such as that associated with thermal burns, an ulcer of the duodenum or stomach may develop (Curling's Ulcer), and it has been repeatedly found that the administration of cortisone and/or ACTH may result in peptic ulceration It was stated by Gray and his associates[31] that these hormones result in a pronounced increase in both acid and pepsin secretion How this effect is mediated is not apparent, for it has been reported that cortisone has no local effect on secretion by gastric cells *in vitro*.[15] Regardless of the mechanism, however, the increased secretion of acid and pepsin following hormonal therapy is not necessarily the cause of the ulcer

The presence of a pheochromocytoma may be first manifested by peptic ulceration and hemorrhage, presumably due to the systemic effects of the increased blood level of epinephrine and norepinephrine Peptic ulceration has been reported in association with functioning parathyroid tumors and with tumors of the pancreatic isles of Langerhans, as has been mentioned above The mechanisms of these relationships have not been defined

Mechanism of Ulcer Pain

There exists a difference of opinion as to the cause of the pain associated with peptic ulcer One theory is that the pain is due to chemical irritation of exposed sensory fibers in an ulcer crater by hydrochloric acid, the acid evokes a chemical inflammation and thereby lowers the pain threshold of the nerve endings that are present in large numbers in the base and in the edges of the ulcer The pain arises only when the gastric contents are acid Even so, the concentration of the acid at the time of distress may not be abnormal, nor need it be greater than that present in the same stomach without pain when the ulcer is healed or in a healing phase Furthermore, the threshold of acidity necessary to evoke pain varies greatly from one patient to another and in the same patient from time to time

In contrast, an opposing theory is that the pain of ulcer is produced by increased muscular activity or spasm at the ulcer site (Fig 116) In 150 consecutive patients studied by Ruffin and Carter[71] with an acid barium mixture at pH 1, only 50 (33 per cent) had pain following ingestion of the acid mixture In addition, the development of pain was associated invariably with altered motility, consisting of incoordination of the gastric evacuation mechanism with or

without localized spasm In 17 patients having a duodenal ulcer no acid barium could be demonstrated in the ulcer crater in many patients who experienced no pain at the time and in some patients having ulcer distress the ingestion of acid barium was followed by immediate relief Finally, relief of pain regularly followed the intravenous *administration of a potent anticholinergic* drug This coincided exactly with cessation of gastric motility as observed fluoroscopically, despite the fact that the pH of the gastric contents remained unchanged It was concluded that for the production and perception of ulcer pain there must be (1) a stimulus, either hydrochloric acid or others less well understood, (2) an intact motor nerve supply to the stomach and duodenum (3) altered gastroduodenal motility, and (4) an intact sensory pathway to the cerebral cortex.

The acid-factor and the motility factor are probably both important in the production of ulcer pain

TRANSMISSION AND CHARACTER OF ULCER PAIN Nerve impulses from the duodenum and gastric region are transmitted over the parasympathetic (vagus), the sympathetic (splanchnic), and the intercostal (somatic) nerves (Fig 117) The vagus nerve is concerned primarily with gastrointestinal motility and secretion, and it is not concerned with carrying sensory impulses of a painful nature This has been shown by stimulating the proximal end of the vagus nerve and causing no *sensation in the conscious* patient and it is further supported by the fact that after complete vagotomy the pain of gallbladder colic or recurrent peptic ulcer is unchanged. In contrast, interruption of the sympathetics abolishes the visceral pain that is produced by distention or spasm of the hollow viscus or by traction upon the mesentery

The pain of an uncomplicated ulcer is located almost always in the epigastrium and is usually limited to an area a *few centimeters* in diameter A duodenal ulcer that is located on the posterior wall may at times be associated with pain referred to the back, particularly if it is a penetrating ulcer Ulcer *distress arising from lesions not penetrating* to the serosa may have a cutaneous reference, and this indicates that visceral nerves *are capable of* mediating referred pain. Pain from marginal ulcer occurring at the gastrojejunostomy stoma following gastric resection may also be referred to the back and may be confused with symptoms arising from pancreatitis or biliary disease

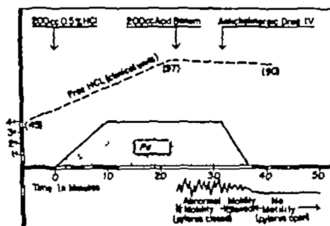


Fig 116 Relationship of acidity motility anticholinergic drugs and pain It is indicated that the pain of the peptic ulcer was abolished by an anticholinergic drug even though the induced gastric acidity remained high Nevertheless, there is disagreement among gastroenterologists as to whether ulcer pain is due to gastric acidity or to gastric motility Probably both are important (From RUFFIN J M AND CARTER, D D Peptic ulcer Disease A Month, Aug 1955 Year Book Publishers Inc., Chicago)

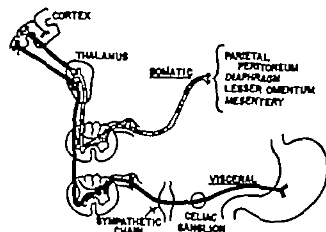


Fig 117 The pain of peptic ulcer (mediated by sympathetics) is abolished by sympathectomy unless the parietal peritoneum (pain mediated by somatic nerves) is irritated (RUFFIN J M., AND CARTER, D D Peptic ulcer Disease A Month Aug., 1955 Year Book Publishers, Inc Chicago)

The clinical picture of an uncomplicated duodenal ulcer is so characteristic that the history is a very important aid in diagnosis The pain usually appears some 2 or 3 hours after a meal, and is relieved by the taking of food or alkali If the ulcer is situated in the pyloric canal (a "channel" ulcer), however, it may give rise to a bizarre syndrome that is quite different from the above picture In an analysis of 100 consecutive patients having channel ulcer, confirmed by x-ray studies or by operation, Ruffin and associates[72] found *nausea and vomiting the most common symptoms*, occurring in 83 per cent of the cases

Gastric vs. Duodenal Ulcer

There has been much discussion regarding whether duodenal ulcer and gastric ulcer, so similar in many important respects, are not, however, fundamentally different diseases. In patients with duodenal ulcer there is usually an elevated gastric acidity, while many gastric ulcers are associated with a normal or subnormal gastric acidity. The patient with duodenal ulcer is usually beset by emotional strain, this is not conspicuous in the subject who has gastric ulcer The duodenal ulcer is almost never the site of malignancy, the gastric ulcer is frequently the site of malignancy In fact, it is estimated that from 5 to 10 per cent of gastric ulcers (Fig 118) represent malignancy

The local factors which fail to withstand the destructive action of acid-pepsin gastric juice would appear to be especially important in the production of gastric ulcers, for here the acid concentration may be normal or even subnormal

In summary, duodenal ulcer is usually associated with an increased gastric acidity, as are many gastric ulcers, however, other gastric ulcers are not associated with an increased acidity and may be due to a fundamentally different etiology



Fig 118 Gastric ulcer This benign lesion was excised *en bloc* with omentum and spleen when malignancy could not be excluded on frozen section The acid-pepsin factor is admittedly important in the genesis of most duodenal ulcers, but many patients with gastric ulcer have a normal or low gastric acidity Hence, gastric ulcer and duodenal ulcer must be considered separately, especially as the former is often malignant and the latter almost never so

Physiologic Principles of Peptic Ulcer Management

Treatment is aimed at reducing the gastric acidity. Since anxiety and mental stress increase the acid pepsin concentration in the stomach, every effort is made to put the individual at emotional rest to diminish the cephalic (nervous) phase of acid secretion. Even by hospitalizing the patient this can usually be accomplished only in part by rest and additional measures are commonly required. Moreover, it has been seen that the cephalic phase normally represents only 45 per cent of the secretion, while the gastric phase also represents 45 per cent, and the intestinal phase, 10 per cent—though the cephalic segment may be the most important in ulcer patients. The additional conservative measures consist chiefly of an "ulcer" diet with frequent feedings, alkaline compounds, mild sedatives, and atropine-like drugs.

The diet should be bland in character. Three main meals with "interval" feedings constitute the usual regimen. The most important feature is to keep the gastric acid neutralized continuously by sufficiently frequent feedings or alkalinizing medication, preventing the stomach from becoming empty and exposing the ulcer to a bath of highly acid gastric juice. In some instances, especially in patients with night pain, feedings may have to be administered around the clock, and it is the practice of some physicians to insert an indwelling nasogastric tube and continuously to drip some neutralizing material into the stomach in severe cases. One former teacher often stated that so long as something was maintained in the stomach constantly, even if it were alfalfa, most ulcers would heal—an overstatement, perhaps, but one that underscores the basic therapeutic requirement. Actually the feedings should contain, when practical, a fair proportion of fat so as to take advantage of its depressant effect upon gastric secretion as well as upon gastric motility. Potent stimulators of gastric secretion such as meat extracts should be avoided in the acute phase, and alcohol should be avoided indefinitely.

Antacids (and food) are employed to raise the pH of the gastric contents above the level necessary for peptic digestion. Pepsin acts best at pH 1.5 to 2.2. Antacids are not necessary in many cases, but they can be used instead of interval feedings if excessive caloric intake results in undue weight gain, and at bedtime in individuals having night pain. When an antacid is used, it should be relatively insoluble and cause neither constipation, diarrhea, or acid rebound.[51]

THE USE OF BELLADONNA AND SIMILAR DRUGS

Banthine and Pro-Banthine are atropine-like compounds with an anticholinergic action similar to that of atropine but with fewer of the undesirable side effects. It has been noted elsewhere that Banthine will diminish pancreatic secretion. It will also diminish the nervous phase of gastric secretion. There are other compounds which may be used, but Banthine (methantheline bromide) and Pro-Banthine (propantheline bromide) are representative of this group. These drugs interfere with the cholinergic transmission of nerve impulses, and they differ from the atropine group in that they are effective not only at the effector site but also at the parasympathetic ganglia. This blockade of parasympathetic impulses results in a so-called "medical vagotomy," with inhibition of both secretory and motor activity of the stomach. In addition to these effects Wolff[91] observed a decrease in the engorgement of the gastric mucous membrane after their administration. Although certain of the undesirable side effects are less severe with Banthine than with atropine, these symptoms are still present in varying degrees and they include the atropine-like visual and salivary disturbances, tachycardia, difficulty in urination, abdominal distention, constipation, and an ill-defined feeling of lassitude or fatigue.

It is generally agreed that the anticho

linergic drugs inhibit gastric secretory activity, with a reduction of both volume and acidity However, the response following oral administration is both variable and unpredictable, and anacidity is not often attained with currently available drugs unless high doses are employed After parenteral administration anacidity occurs somewhat more frequently but, unlike vagotomy, these drugs have little effect on the cephalic phase of acid secretion

The effect of Banthine on gastrointestinal motor activity is generally more pronounced and less variable than is the effect of Banthine on gastric secretion [47] In the normal person there is no demonstrable effect on the motility of the esophagus as determined by roentgenography, but balloon studies have shown a reduction in spontaneous motility of the esophagus after Banthine was given intravenously This agent does not relax the cardiac sphincter, and the administration of these drugs in patients with cardiospasm aggravates the condition, as does vagotomy [73] The most striking clinical effect of these agents has been the relief of ulcer pain, an effect that is frequently dramatic after parenteral administration This relief of pain may be synchronous with the cessation of gastric motility despite artificially high acid values [46] Nevertheless, the abolition of pain is not necessarily indicative of healing, for ulcer craters have been observed to persist for weeks or months under treatment even though the patient was symptom-free Few data are available regarding the effect of these drugs on the healing time of ulcers

Actually, Banthine and Pro-Banthine have been disappointing in the long-term management of ulcer Recurrences have not been prevented and the incidence of complications or the need for surgery have not been significantly altered by prolonged administration These drugs are not often required in the management of the simple uncomplicated ulcer

A commonly used dosage of Banthine is from 50 to 100 mg every 6 hours

Complications of Peptic Ulcer

Surgery should be reserved for the management of the complications of duodenal ulcer, since this ulceration is primarily a nonsurgical disease

FAILURE TO RESPOND TO MEDICAL TREATMENT Some patients with peptic ulcer remain unsatisfactorily managed even after a carefully controlled and prolonged period of medical therapy, and in such individuals (whose incidence is inversely proportional to the quality of medical treatment) surgery may be required to control the acid-pepsin secretion Surgery does not abolish the personality structure which predisposes to peptic ulceration, however

PYLORIC OR DUODENAL OBSTRUCTION A second complication which requires surgery is that of obstruction caused by the chronic inflammation which finally leads to fibrous stenosis of the gastric outlet In this instance the primary purpose of surgery is to relieve obstruction, but if the previous ulcer is not "burnt out" and significant acid formation continues, then measures must also be taken to reduce the acid-pepsin factor to lower the probability of further ulceration For example, simple gastroenterostomy may be followed by stomal (marginal) ulceration; vagotomy or subtotal gastric resection must be employed to reduce gastric acidity, if indicated on the basis of the preoperative gastric analysis In younger individuals such additional procedures will usually be necessary but in elderly patients, whose gastric acidity usually has declined, they may not be

HEMORRHAGE Duodenal ulcers that bleed are usually situated on the posterior or medial walls, since it is here that major vessels enter and may be eroded, the superior pancreaticoduodenal artery being most important In contrast, ulcers which perforate are usually located on the anterior surface of the stomach or duodenum, since here there are no coapted tissues which limit free leakage

Gastroduodenal hemorrhage and hepatic blood flow Massive hemorrhage from the

upper gastrointestinal tract may have an especially serious effect on liver function, in addition to the other ever present deleterious effects of significant bleeding. Le Veen, Mulder, and Prokop[48] showed that bleeding from the gastroduodenal artery (a branch of which is the usual source of bleeding in duodenal ulcer) caused the pressure in the hepatic artery to fall much more rapidly than did an identical amount of hemorrhage from a femoral artery. This *selective reduction of hepatic blood flow in gastroduodenal hemorrhage* was greatest when the systemic blood pressure reached levels below 100 mm. Hg. With one cannula tied into the dog's gastroduodenal artery and another in the left femoral artery, these workers produced rapid bleeding from both of these vessels, meanwhile measuring the blood pressure and blood flow in both arteries. When the bleeding was from the gastroduodenal artery, the hepatic arterial pressure dropped to 50 mm. Hg. while that in the femoral artery was maintained at 75 mm. Hg. This differential was not noted when the bleeding was from the femoral artery. Upon measuring blood flow instead of the blood pressure, the difference was even more striking. During rapid gastroduodenal bleeding at a time when the hepatic flow had completely ceased, the femoral arterial blood flow was reduced by only one-third. The hepatic blood flow ceased entirely when the hepatic arterial blood pressure was approximately 60 mm. Hg.

Mortality associated with gastric vs duodenal bleeding. Saltzstein and his associates[74] reviewed 402 cases of massive upper abdominal hemorrhage, which comprised 5 years' experience at Harper Hospital. There were 343 cases of peptic ulcer (69 per cent duodenal, 13 per cent gastric, 3 per cent marginal) and 59 cases (15 per cent) of undiagnosed upper gastrointestinal bleeding. Hemorrhage accounted for 25 per cent of all admissions for peptic ulcer and of these 10 per cent were severe, shock being prevented only by the administration of at least 500 ml. of blood every 8 hours. Of the 343 patients with peptic ulcer, 80 per cent were treated medically and the remaining 20 per cent surgically. Of those treated surgically, 80 per cent were mild bleeders and many of them had bled previously. There were 4 (5.9 per cent) surgical deaths. The medical mortality was 5.1 per cent, half of these deaths occurred in mild bleeders, and since several of them had had associated cardiovascular conditions it was considered possible that the anoxia of gastrointestinal hemorrhage may have precipitated cardiovascular accidents. Three of the 14 patients who died while under medical management died in shock due to uncontrolled hemorrhage. Two of the total 18 deaths occurred in patients aged 45 or under. Of the total 402 patients (343 with peptic ulcer) 50 per cent had hematemesis and 50 per cent had melena alone. Yet, of the 18 who died, 14 (78 per cent) had hematemesis and only 4 (22 per cent) had melena alone. Thus, hematemesis appeared to indicate a more serious prognosis than melena alone. Only 5 of the 343 patients had associated perforation, but in some reported series the incidence of associated perforation has been considerably higher.

Deaths from bleeding gastric ulcer were 3 times as frequent as those from duodenal ulcer and about half the fatalities occurred during the first episode of bleeding. Saltzstein and his co-workers emphasized the need for vigorous transfusional therapy to prevent anoxia of the liver, primarily, but also of the myocardium and the brain.

PERFORATION OF PEPTIC ULCER. Still another complication of peptic ulcer is that of perforation. This results in a chemical and, to an extent, a bacteriologic peritonitis. As we have seen, soiling of the free peritoneal cavity is particularly likely to occur when the ulcer involves the anterior surface of the stomach or duodenum, since these areas are not covered with surrounding tissue unless the omentum adheres. Penetrating ulcers on the posterior surfaces are more prone to be sealed off by the peritoneum of the lesser peritoneal sac or the pancreas, respectively.

In free perforation the clinical findings are usually those of severe upper abdominal pain This distress often prostrates the individual, and results in marked involuntary spasm or rigidity of the upper abdominal musculature Presently the pain and tenderness may spread downward, as the escaping gastric contents flow into the right gutter, and this may simulate the pain of appendicitis In fact, it is not rare that, having first made a McBurney incision on the presumptive diagnosis of acute appendicitis, the surgeon encounters gastric fluid (or palpates an acutely inflamed gallbladder) He must then extend the incision upward or, preferably in our view, close the McBurney incision and make a separate incision above

At times there may be pain in the shoulder due to irritation of a leaf of the diaphragm by the gastric fluid, and properly taken roentgenograms will reveal free air in the peritoneal cavity in more than 50 per cent of the cases

Serum amylase in perforated ulcer Numerous observations have now confirmed the fact that the serum amylase concentration is frequently elevated in the presence of an acutely perforated peptic ulcer

The sequelae of perforation In a review of 136 cases of perforated peptic ulcer (34 gastric, 97 duodenal, and 5 marginal) treated at the King County Hospital (Seattle) during a 5-year period from 1948 to 1952, Schmitz and his associates[75] found that a large proportion of these patients were chronic alcoholics with other serious pathologic conditions Perforation of a gastric ulcer was a much more serious condition than was perforation of a duodenal ulcer, the mortality in surgical cases being 16 6 per cent and 2 7 per cent, respectively Since recurrence or persistent ulceration was frequently found in their patients, it was felt that elective subtotal gastrectomy within 8 weeks after perforation was advisable in selected cases Moreover, these findings were in accord with those reported by Stabins,[60] who found that major sequelae developed in 65 1 per cent of 167 cases of perforated duodenal ulcer, definitive surgery became necessary in 36 5 per cent of these

Management of perforated ulcer The traditional method of treatment for perforated ulcer was simple surgical closure, this was highly successful In recent years, however, two new trends have developed, in opposite directions On the one hand, increasing numbers of physicians are managing perforated ulcer conservatively, with antibiotics, intravenous fluids, and continuous nasogastric suction—and most of these patients recover On the other hand, some surgeons now prefer to do emergency gastric resection instead of merely closing the site of the perforation

We hold definite views concerning both trends Regarding the conservative management of perforation, it is possible that the *mortality* associated with medical management may not be substantially greater than that with surgical management, but we believe that the *morbidity* has also to be reckoned with—and certainly more extensive peritonitis and a greater number of residual abscesses will follow conservative management Therefore, my personal opinion is that, where adequate surgical facilities exist, operative closure of the perforation should be performed, at least at the present time This opinion was considerably stiffened by the course of a patient who, because of numerous other complicating factors, I elected to treat conservatively Perforation occurred while he was being studied for high fever associated with an extensive necrotizing lesion of the mouth and pharynx, and he had long been treated for opiate addiction and alcoholism There was a typical clinical picture of perforation, and free air was present under the diaphragm Nasogastric suction and other supportive measures were instituted and his condition steadily improved, so much so that on the fifth day following perforation the gastric tube was removed and oral intake of fluids was begun This was followed by renewed pain and, though all conservative measures were renewed and intensified, he died several days later At autopsy a perforation was found on the an-

terior surface of the duodenum and another on the posterior surface of the stomach. Both communicated freely with the greater peritoneal cavity and lesser sac, respectively, and there was no evidence of healing or of closure by omental migration. While admittedly this patient, who had a striking septic fever without leukocytosis, represented an unusual problem, I shall not soon again employ conservatism in the management of perforated peptic ulcer Where the condition of the patient is considered to be too critical for general or spinal anesthesia local anesthesia can be used to close the perforation

MANAGEMENT OF GASTRIC ULCER. *Malignant degeneration of gastric ulcer* One further complication is that of malignant degeneration of gastric ulcer It is still a moot question, in our opinion whether a gastric ulcer degenerates' into carcinoma or was malignant from its inception, yet, there is evidence to suggest that occasionally cancer can develop in a chronic gastric ulcer, as it can in chronic ulcers on the body surface In any event if the gastric ulcer does not heal promptly (4 weeks for example) under medical therapy we believe it should be resected, particularly in patients over fifty Smith Boles, and Jordan[79] analyzed 1000 cases of gastric ulcer treated at the Lahey Clinic and concluded that a period of one month or less of intensive medical management was justified since the operative mortality following gastric resection for benign ulcer was perhaps greater than the mortality that resulted from undiagnosed malignant ulcer

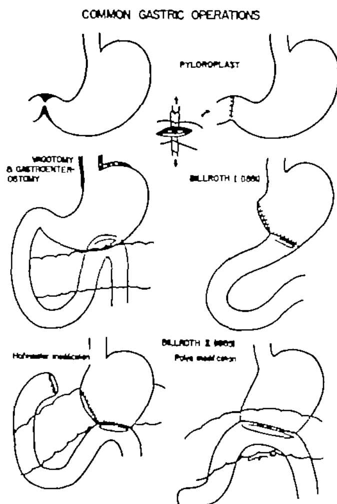


Fig 119 Pyloroplasty is used alone only for the correction of pyloric stenosis and where the reduction of gastric acid secretion is not an objective Vagotomy-gastroenterostomy is the surgical treatment of choice for peptic ulcer in some clinics The Billroth I operation has recently been revived Some modification of the Billroth II is the choice of a majority of surgeons in the United States

Operations for Peptic Ulcer—Physiologic Pros and Cons

Some of the common procedures that are employed in the surgical management of peptic ulcer are shown in Figure 119 Others of historic interest are shown in Figure 120

GASTROENTEROSTOMY [41] The first gastrojejunostomy for peptic ulcer is said to have been performed by Wolfler of Prague in 1881 However it was Lord Moynihan who brought this operation into world prominence as a means of partially diverting the acid stream from the duodenal ulcer and of altering gastroduodenal motility Unfortunately ulceration at the gastrojejunal stoma occurred with such frequency that gradually the operation lost favor until now it is rarely employed except in patients whose gastric acidity is low Furthermore, persistence of the duodenal ulcer and the development of gastrojejunocolic fistula secondary to the stomal ulcer, constituted undesirable aspects of simple gastrojejunostomy as the sole means of duodenal ulcer management.

SUBTOTAL GASTRIC RESECTION This procedure, first performed by Theodor Billroth[4] in 1881 was based upon the physiologic

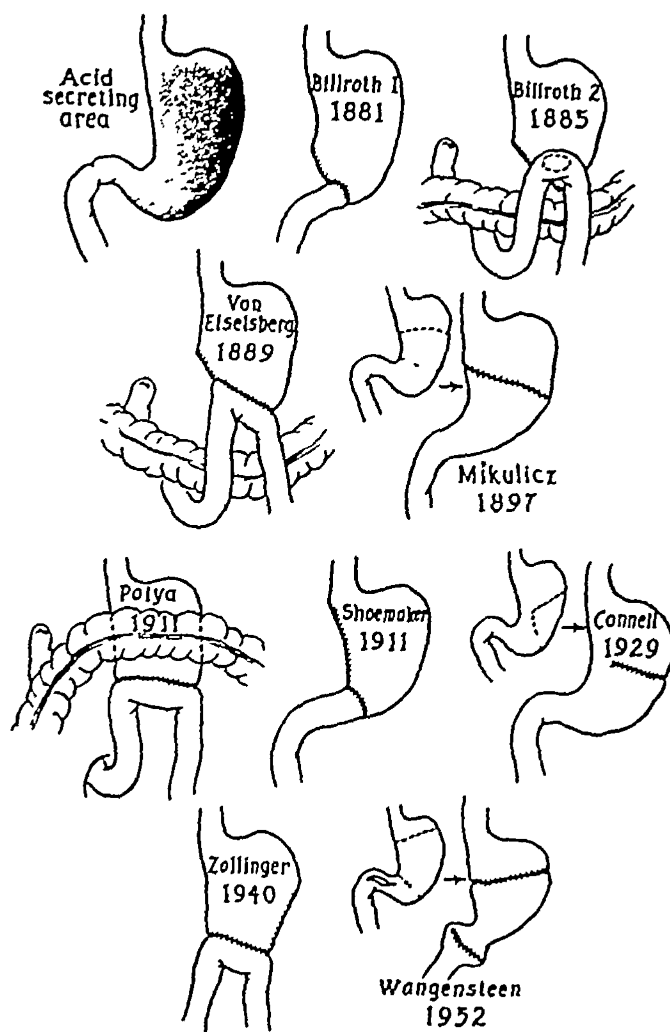


Fig 120 Location of acid-secreting cells in stomach and methods of subtotal gastric resection The rich and dependable vascularity of the stomach has permitted many innovations (From NAGEL, G W Subtotal *gastric resection for peptic ulcer* Calif Med, **78**· 190, 1953)

facts that hydrochloric acid is secreted by the cells of the fundus and body of the stomach and that an important stimulus to their function is the passage of food across the antrum Early gastric resection consisted chiefly of excision of the pylorus with antrumectomy, since it was considered that if the hormone gastrin were removed the secretion of acid and pepsin by cells of the body of the stomach would be diminished As with gastrojejunostomy, however, clinical experience soon showed that the removal of only the lower third of the stomach did not result in a sufficient reduction of the acid-pepsin secretion to manage the ulcer diathesis successfully in most cases It is now known, of course, that this removal of only the hormonal phase of gastric secretion left the nervous and the intestinal phases still intact (Fig 112)

During the early 1940's there was a progressive tendency to remove more and more stomach, often from 70 to 90 per cent, and this did satisfactorily reduce the amount of acid secreted However, it was eventually evident that the removal of from three-fourths to four-fifths of the stomach frequently resulted in most undesirable sequelae, such as the dumping syndrome and an inability of the patient to regain or even to maintain his weight For this reason some further approach was sought, and in 1943 Dragstedt re-introduced vagotomy to control the cephalic phase of gastric secretion, a phase which had heretofore been treated with atropine and similar drugs

VAGOTOMY, WITH OR WITHOUT GASTROENTEROSTOMY OR PYLOROPLASTY Vagotomy (division of the vagus nerves) may be performed transthoracically or transabdominally Though exposure is more difficult, the abdominal route has the advantage of permitting simultaneous gastroenterostomy or pyloroplasty—which most now agree is necessary if gastric stasis is to be avoided The stasis is due to diminished gastroduodenal tone and to various degrees of organic stenosis from ulceration and scarring

Vagotomy relieves ulcer pain almost at once, probably because of decreased gastroduodenal motility—for it was pointed out previously that artificial elevation of gastric acidity will often not cause pain recurrence following vagotomy If pain is not relieved, the completeness of the vagotomy should be checked with the insulin test Some "dumping" does occur following the operation of vagotomy plus a drainage procedure, but it is perhaps less common than following the Billroth II gastric resection with gastrojejunostomy

At first vagotomy was widely employed in the management of duodenal ulcer, but at the present time its rôle in American surgery is confined largely to the management of the marginal ulcer following gastric re-

section, to the management of poor risk patients, and to instances where gastric resection would be technically hazardous, perhaps to the common bile duct. Yet, some very competent surgeons employ vagotomy gastroenterostomy as the primary surgical procedure for duodenal ulcers in almost all patients. In actively bleeding ulcers gastric resection may be required to control the hemorrhage and some type of resection is always indicated for gastric ulcers

VAGOTOMY WITH GASTROENTEROSTOMY—OTHER CONSIDERATIONS. The several types of gastric resection will be considered further presently but at this point it is desirable to take further cognizance of the continuing dispute regarding whether or not vagotomy with gastroenterostomy (or pyloroplasty) or subtotal gastric resection is the better method of treating duodenal ulcer surgically (aside from the special indications for vagotomy given above) After the operation of vagotomy with gastroenterostomy had been thoroughly studied in various surgical centers for approximately 5 years, a special committee was appointed by the American Gastroenterological Association to compare the result of subtotal gastric resection with vagotomy-gastrojejunostomy, and to present a critical analysis of the two procedures in the surgical management of peptic ulcer The results of vagotomy alone gastroenterostomy with and without vagotomy, and subtotal gastric resection with and without vagotomy were compared with respect to the value of each in the treatment of duodenal and gastrojejunal ulcer [43] The report was based upon 4076 cases of peptic ulcer The final conclusion was that gastric resection for duodenal ulcer has an advantage over vagotomy and gastroenterostomy only if there is an estimated resection of more than 70 per cent of the stomach.

There is no question that vagotomy-gastrojejunostomy is attended by a lower mortality rate than is gastric resection.

Everson and co-workers[26] made a comparative nutritional follow up study of 318 patients subjected to partial gastrectomy (Billroth II) and 118 patients subjected to vagotomy with gastroenterostomy Although weight loss tended to occur more frequently and more severely after partial gastrectomy, the differences in the percentage of patients who lost an appreciable amount of weight after partial gastrectomy and after vagotomy with gastroenterostomy were not great The data confirmed the frequently expressed clinical impression that the incidence and severity of loss of weight increase directly with the extensiveness of the gastric resection Patients who preoperatively were below "ideal weight tended to have less deficit in weight after vagotomy with gastroenterostomy than after partial gastrectomy

An extensive experience with vagotomy was reported by Grimson and his associates [32] They found that the beneficial effects of vagotomy in their patients usually persisted and that insulin tests performed from 3 to 7 years after vagotomy produced no free acid or less free acid than control patients in 25 of the 26 vagotomized patients tested. This would tend to cast doubt upon the common impression that the sectioned vagus nerves regenerate It was further emphasized that patients treated by vagotomy gastroenterostomy maintained their weight far better than those treated by the Billroth II gastric resection (However, it will be seen below that patients having the Billroth I gastric resection maintain their weight better than those having the Billroth II operation and perhaps as well as those having vagotomy gastroenterostomy)

The incidence of persistent diarrhea is approximately 2 per cent for both gastric resection and vagotomy gastroenterostomy, and the incidence of dumping is also approximately equal with the two procedures

TYPES OF GASTRIC RESECTION In deciding upon the particular type of operation to be performed the surgeon must take into consideration (1) the *site* of the ulcer (adjacent to the common bile duct? in the stomach?) (2) the character of the *pathologic lesion*

(if malignant, extensive resection), (3) the associated *mechanical disturbances* (pyloric obstruction?), (4) the resultant *metabolic disturbances* (repair water and sodium chloride depletion, potassium deficiency, and metabolic alkalosis), and (5) the *age* of the patient (the physiologic margin of safety in the elderly is thin)

Since it became apparent that gastric resection was to be preferred to simple gastroenterostomy, a considerable variety of different types and degrees of gastric resection have been proposed and employed clinically (Fig 120) However, it is not the purpose here to debate the merits of many different procedures Rather, we shall limit the present discussion to the Billroth I and modifications of the Billroth II subtotal gastric resection References to other technics are given in the bibliography A standard method for testing the efficacy of new operations is to study their protective effect against histamine-in-beeswax-induced ulcers in dogs[11]

The relative merits of the Polya modification of the Billroth II as compared with the Hofmeister modification of the Billroth II (Fig 119) In our opinion, there is no great difference between the results achieved with the Hofmeister as compared with the Polya modification of the Billroth II While the Polya procedure does involve anastomosing the entire width of the divided stomach to the jejunum, whereas the Hofmeister procedure employs only that portion (3–4 cm) adjacent to the greater curvature (the remainder of the severed stomach adjacent to the lesser curvature being closed separately), to a considerable extent it is the width of the jejunal lumen which limits the rate at which gastric chyme enters the small bowel Some observers have thought that dumping is definitely more frequent following the Polya anastomosis, but one doubts if the difference in incidence is marked Gastric retention has also been reported to be slightly more common following the Polya operation than the Hofmeister, due to the "neurogenic syndrome" of the distal loop (p 320) Apropos of this question, Glenn and Harrison[29] reported their experience with 100 cases of gastric resection performed for ulcer during 1948, and 14 instances of "gastric retention" were found The retention was described as occurring from 1 to 14 days following operation in 11 of the 14 cases, in the other 3 cases the latest time was 30 days Of the 100 cases discussed, the Polya type operation was used in 73, the Hofmeister in 20, and other methods in the remaining 7 cases All of the 14 patients who had retention had had the Polya type of anastomosis

Billroth I vs Billroth II During recent years there has been a marked resurgence of interest in the Billroth I operation Essentially, this procedure usually consists of partial gastric resection, partial closure of the divided stomach adjacent to the lesser curvature, and anastomosis of the remaining gastric stoma to the duodenum (*Fig 119*)

What are some of the arguments pro and con of the Billroth I vs. the Billroth II operation? The following points will be considered (1) *simplicity of operative procedure*, (2) *mortality and complications*, (3) *the control of the ulcer diathesis*, and (4) *the nutritional status* of the individual following resection

Simplicity of the operative procedure There is no question that, particularly in patients whose duodenum is suitable, the Billroth I procedure is somewhat more easily and rapidly performed than the Billroth II No sooner is the first portion of the duodenum freed-up, and the ulcer and a sufficient amount of stomach resected, than one is ready partially to close the transected stomach and to anastomose the remaining aperture to the duodenum—and in a majority of duodenal ulcers and virtually all gastric ulcers this can be done The duodenal "stump" problem is avoided, and the time usually employed in closing the duodenum is conserved

Mortality The mortality following the Billroth I operation has often been reported to be slightly less than that following the Billroth II Wallensten and Gothman[56] re-

corded an operative mortality of 2.2 per cent in 364 cases having the Billroth I procedure (1.2 per cent for duodenal ulcer and 4.9 per cent for gastric ulcer) the incidence of recurrent ulceration was 3.7 per cent for duodenal ulcer. In a series reported by Harkins and his associates,[56] the mortality in the Billroth I series was 3.8 per cent (100 patients operated upon) and that in the Billroth II group 7.4 per cent (135 total patients). This mortality for the Billroth II operation is a bit higher than usual, though many of their patients were in poor condition preoperatively.

While it is too soon to assess accurately what the comparable mortality following the two procedures will be, when applied consecutively in similar groups of patients, it would appear that the mortality following the Billroth I procedure is lower, possibly because a gastrojejunal anastomosis with potential kinking and obstruction is not present to increase the risk of duodenal stump "blow out." This complication has always constituted a major source of mortality after Billroth II procedure. Incidentally prominent sources of duodenal stump" complications are inadequate remaining blood supply, closure using inflammatory or devitalized tissue, inadequate inversion or other technical deficiency, and obstruction at the proximal gastric stoma.

Recurrence of ulcer. In Harkins' series there were as yet no known recurrent ulcers in the Billroth I group, but there were three known and two possible recurrent ulcerations in the Billroth II group.

There appears to be general agreement that gastrojejunal ulceration occurs in from 1 to 5 per cent of cases following subtotal gastrectomy. The reason that ulceration apparently has not occurred in as large a number of cases following the Billroth I procedure may be due to the fact that, as shown experimentally, the presence of acid (and fat) in the duodenum exerts an inhibitory effect on the secretion of acid by the stomach; it also stimulates the duodenal mucosa to elaborate secretin, which produces the secretion of the alkaline pancreatic juice. Another factor in the (reported) rather low incidence of ulceration following the Billroth I procedure may be the fact that the duodenal mucosa has been shown to be more resistant to acid pepsin digestive activity than is the jejunal mucosa.[17] Finally, the Billroth I operation places the stoma of the anastomosis nearer the alkaline bile and, as noted, the alkaline pancreatic juice.

Even so, one should for the present reserve judgment regarding the relative incidence of ulcer recurrence following the Billroth I and the Billroth II operations. In time, additional patients who had the Billroth I operation may exhibit this complication.

Incidence of "dumping." It is agreed that the incidence of dumping is approximately the same for the Billroth I and II procedures, ranging from 15 to 25 per cent following greater than 70 per cent resection.

Comparison of nutritional disturbances following the Billroth I and Billroth II procedures. A number of careful studies have now been reported regarding the nutritional disturbances which follow gastric resection and recently there has been an opportunity to compare the derangements following Billroth II with those following the Billroth I procedure. The general consensus is that the Billroth I procedure causes somewhat less derangement in normal digestive processes than does the Billroth II. It is well known that one of the major causes of dissatisfaction with the Billroth II operation is that so many patients have difficulty maintaining their weight. In contrast, after the Billroth I procedure patients are not so likely to lose weight and, in fact, many regain weight. This difference was shown by Wollaeger[62] to be related to the fecal loss of fat and nitrogen. He found that in 8 patients who had had the Billroth I procedure an average of 12.3 gm. of fat was excreted in the feces per day, as compared with an average of 19.9 gm. of fat in 10 patients who had had the Billroth II operation. Such a difference may be due to the fact that normal gastrointestinal continuity promotes the

proper mixing of the food with bile and pancreatic juice in the duodenum. Moreover, it has been shown that pancreatic secretion is diminished following Billroth II subtotal gastrectomy in dogs. Therefore, greater pancreatic secretion might be anticipated after a subtotal gastrectomy in which the food passes into the duodenum (Billroth I and segmental types) than after one in which the food passes into the jejunum, the production of secretin in the duodenum is greater than in the jejunum.

In a review of the literature, Everson[25] found that in 43 metabolism studies of 35 patients after a Billroth II type of subtotal gastrectomy there was impairment of fat assimilation in 23 of the 35 patients. Likewise, following the Billroth II operation there was impairment of protein assimilation in 11 of 36 collected patients. According to Ivy, Grossman, and Bachrach,[37] who collected 864 cases from the literature, 42 per cent of the patients having subtotal gastric resection (Billroth II) for peptic ulcer had a late postoperative weight that was less than the normal preoperative weight. In contrast, Wallensten and Gothman[86] found that only 14 per cent of 364 patients having the Billroth I operation failed to maintain their weight.

An additional type of evidence to support the Billroth I operation has been advanced by Perman.[66] In 25 patients in whom there were nutritional and other disturbances following the Billroth II procedure, he reoperated and converted the anastomosis to the Billroth I type, 23 had excellent results, 1 had a poor result, and 1 death occurred following secondary operation.

The experimental study of Everson[25] was further revealing. He conducted a careful comparison of protein and fat assimilation after the Billroth II, Billroth I, and segmental types of subtotal gastric resection. The dogs having the Billroth II type of subtotal gastrectomy (75 to 80 per cent of the stomach) excreted in the feces an average of 24.4 per cent of the ingested nitrogen, as compared with 19.3 per cent in 10 dogs subjected to Billroth I gastrectomy, 12.6 per cent in 10 dogs subjected to segmental gastrectomy, and 14.9 per cent in normal animals. An average of 27.7 per cent of the ingested fat was excreted in the feces of 10 dogs subjected to the Billroth II type of subtotal gastrectomy, as compared with 10.6 per cent in 10 dogs subjected to Billroth I gastrectomy, 6.4 per cent in 10 dogs subjected to segmental gastrectomy, and 4.9 per cent in normal animals. The majority of animals subjected to the Billroth II operation lost weight on an *ad libitum* diet, while the majority of animals subjected to Billroth I and segmental types of subtotal gastrectomy gained weight or maintained their weight on a similar diet. In general, the nutritional status of animals subjected to the Billroth II type of subtotal gastrectomy was markedly inferior to that of animals subjected to Billroth I and segmental types of subtotal gastrectomy. Nutritional status after the segmental type of subtotal gastrectomy was essentially normal, and whereas the nutritional status after Billroth I type of subtotal gastrectomy was somewhat inferior to that following the segmental type, the differences noted were not great. In a supplementary study, Javid[40] found that vagotomy-gastroenterostomy was superior to the Billroth II Polya operation, in so far as fat and nitrogen intake-excretion studies were concerned.

Billroth I, vagotomy-gastrojejunostomy, and Billroth II—concluding comment. As will be seen, then, there is much evidence to indicate that in many respects either the Billroth I or vagotomy-gastrojejunostomy is superior to the Billroth II. Yet, the majority of surgeons continue to use the last almost routinely. Why is this so? It is because surgeons found, after disillusionment with simple gastroenterostomy, that the orthodox Billroth II subtotal gastric resection was an operation which provided an effective means of controlling the ulcer diathesis in most patients. It will not be superseded until another procedure has been proved superior by the same demanding test.

COMPLICATIONS OF GASTRIC RESECTION. The

complications which may follow gastric resection are numerous and a number of them (some of which have been discussed previously) may be listed

A. *General*
  1 Dumping syndrome (including vasomotor symptoms, distention, vomiting, or diarrhea)
  2 Failure to maintain or to regain weight
B *Failure of proximal loop or gastric remnant to empty properly following the Billroth II operation*
  3 Proximal loop obstruction at proximal stoma (pain, nausea intermittent vomiting of copious amounts of bile)
  4. Obstruction of distal stoma (due to technic, kinking, or edema)
  5 Suturing of the transverse mesocolon to the jejunum instead of the stomach in a posterior anastomosis
  6 'Neurogenic syndrome of distal loop
  7 Adhesions involving upper jejunum
  8 Herniation of small bowel beneath jejunal loop in anterior anastomosis
  9 Intussusception of distal jejunal loop
  10 Abscess surrounding the anastomosis
  11 Pancreatitis
C *Blowout of Duodenal Stump*
D *Marginal ulceration with bleeding, perforation, or gastrojejunocolic fistula*

The dumping syndrome The incidence of this complication has been given but it is pertinent to consider here the nature of this condition. Typically, shortly after a meal the susceptible patient may experience profuse sweating nausea and weakness, and may be forced to lie down. Such symptoms may persist for months and then be replaced by diarrhea The symptoms can be reproduced in the susceptible individual by instilling a hypertonic solution of sucrose or magnesium sulfate into the upper small bowel

Fluid drawn in from the bowel wall Peristalsis moves the ingested food through the bowel so rapidly that there is not time for large volumes of fluid to be drawn into the bowel from the extracellular space

The precise cause of the symptoms of the dumping syndrome is still uncertain, though we are inclined to favor the explanation offered by Randall and his associates,[70] they demonstrated a sharp fall in plasma volume during the period of most intense symptoms and certainly most of the symptomatology is compatible with incipient oligemic shock. Other explanations that have been offered are hypokalemia (which can be demonstrated) and hypoglycemia Webber, Bender, and Moore[83] reviewed the evidence available, including studies of their own They concluded that it was "unlikely that either the fall in plasma volume or the hypokalemia is a significant factor in the etiology of the dumping syndrome, but that both represent physiologic phenomena occurring as a result of the altered anatomy attendant upon gastrectomy"

Weight loss following gastric resection Patients who are excessively thin before gastric resection should probably have either the Billroth I operation or vagotomy gastroenterostomy for a majority lose further weight after the Billroth II procedure

The proximal loop We have observed two cases of proximal loop obstruction that were most instructive The first patient was a woman who had had an extensive resection for a large ulcer high on the lesser curvature She developed a left subdiaphragmatic abscess extending behind the anastomosis displacing the proximal loop anteriorly and kinking it on the small remaining gastric remnant. Roentgen studies with barium revealed a greatly distended proximal loop which at laparotomy was decompressed and anastomosed to a loop of upper jejunum without event. Incidentally she was readmitted months later with a jejunocolic fistula and eventually died after

a lengthy series of various complications which included thrombosis of the inferior vena cava She had been a known morphine addict for years

The second patient was a man who had had a gastric resection followed by a temporary pancreatic fistula, as indicated by a high amylase level in the stab wound drainage He was discharged without further event, though, and was well for about four months, at which time he was rather suddenly seized one day with severe pain in the upper abdomen, associated with the rapid development of a mass readily visible through the thin wall of the epigastrium The nature of the mass was uncertain but, since it did not pulsate, it was judged to be in some way secondary to the previous gastric resection At laparotomy the mass proved to be a tightly distended proximal loop. The operator considered that adhesions had caused the obstruction, and these were lysed However, even then he had some doubt that the adhesions visualized constituted the sole cause of the obstruction, and subsequent events amply confirmed the justification for such misgivings Nevertheless, the abdomen was closed at the time, and the patient's progress carefully followed; after all, the loop had promptly decompressed following division of the adhesions Unfortunately, the patient did not recover so readily as was hoped for, and approximately 10 days following operation he was seized with sudden excruciating pain in the upper abdomen Emergency exploration revealed that the wall of the proximal loop was gangrenous and had perforated at multiple points, producing peritonitis The patient died within 24 hours

This case but again demonstrates that seriously distended bowel must be surely decompressed At the first operation the proximal loop should have been anastomosed to a jejunal loop distal to the stomach, or else the entire gastrojejunal anastomosis should have been taken down

Lorber and Shay[49] made a ... afferent loop following Billroth ...

using a tube through which barium was instilled Among the lesions demonstrated wer persistence of a duodenal ulcer that had no been resected at operation, duodenitis, an a stomal ulcer

Gastric retention following resection Most of the causes of poor gastric emptying listed above are essentially self-explanatory and require only brief comment If the dista stoma is critically narrowed by the inversion of excessive tissue at the time of operation then little edema of the bowel wall is required to occlude the stoma completely

Another serious defect in technic is that of suturing the mesocolon to the jejuna loop instead of to the stomach in a posterior anastomosis The degree of obstruction which may result is just enough to produce gastric retention with inadequate nutrition Moreover, the etiology of the obstruction may be particularly difficult to establish, since barium may pass through the distal stoma These patients may exhibit extreme malnutrition, since some fluid does pass through to achieve a degree of hydration over a prolonged period (Fig 121) The physiology of bowel compression here is not unlike that encountered in congenital malrotation where the lateral peritoneal attachments of an undescended cecum partially obstruct the duodenum

Herniation of the small bowel beneath the jejunal loop is a rare but definite complication, and intussusception of the upper jejunum may occur, as may adhesions, of course

The "neurogenic" syndrome of the distal loop is a particularly intriguing derangement We first encountered it some years ago in a nurse who had had an anterior Polya resection for duodenal ulcer Following operation the stomach did not empty for four weeks, despite the fact that some barium did pass into the distal loop Finally, th ... felt he must re-explore the abdo... no defect was demonstrated— ... and the distal stomas were ... ten ... ever, postopera... not function

and at a third operation some weeks later the anastomosis was resected and another established, again, however, no anatomic defect was found The patient eventually died and still no organic explanation for bowel dysfunction was revealed at autopsy

At that time this was all quite mystifying, but in recent years several reports have indicated that the neuromuscular activity of the bowel may be disturbed by an anastomosis and particularly by the Polya anastomosis Golden[30] reviewed the evidence for this functional obstruction of the efferent loop of jejunum following partial gastrectomy and demonstrated spasm of this loop radiologically The symptoms in the patients he studied were epigastric fullness nausea, and vomiting beginning during the second postoperative week in the great majority of cases These findings usually disappeared spontaneously in a few days but occasionally persisted for several weeks X ray examination disclosed spasm of the efferent loop of jejunum when the symptoms were present, with delay in emptying of the gastric pouch It appeared that the disorder occurred less frequently with the shorter jejunal incision used with the Hofmeister operation than with the longer one used for the Polya operation.

This syndrome may be more common than has previously been realized. Incidentally Urecholine given in 5 to 10 mg doses orally before meals is at times helpful in improving gastric motility and emptying

Blowout of duodenal stump It was stated previously that the most frequent causes of this very serious complication are inadequate technical closure of the duodenum at surgery and obstruction of the proximal loop at the stomach Peritonitis from duodenal leakage is a major cause of mortality following gastric resection.

Gastrojejunocolic fistula This formidable complication is characterized by loose stools (often containing unchanged food ingested only a few moments previously) by foul eructations, and occasionally by the vomiting or regurgitation of frankly fecal material



Fig 181 A result of poor gastric emptying This man had already regained 10 lb when this photograph was taken In the course of a gastric resection and posterior gastrojejunostomy 2 months previously the transverse mesocolon had been sutured to the collapsible jejunal loop rather than to the more rigid stomach Since compression rather than complete mechanical block existed just enough fluid passed to preserve life while permitting slow starvation. Barium could be made to pass out of the stomach promptly The mesocolon was detached and sutured to the wall of the stomach and he had no further vomiting and gained 30 lb There are many reasons why the stomach may not empty following gastric resection (p 319)

(from the colon) Severe weight loss, anemia and hypoproteinemia develop due to both anorexia and the loss of small bowel absorptive surface through the gastrocolic by pass.

The defect usually has resulted from marginal ulceration secondary to a gastroenterostomy (Fig. 119), though at the time of exploration no active ulcer may be found. We prefer to achieve the best possible

preoperative preparation and then to resect the fistula at one stage—re-establishing colon and jejunal continuity, removing additional stomach, and performing gastrojejunal anastomosis distal to the site of jejunal closure where the fistulous portion was excised

Acute gastric dilatation[19] is no longer common, but it does occur and can prove fatal

TOTAL GASTRECTOMY *Anemia* An anemia of varying severity is usual Paulson and Harvey[63] studied the effects of total gastrectomy on erythropoiesis in 27 patients at varying intervals over a decade, and found the following evolutionary sequences First, an iron deficiency anemia resulted shortly after operation, because blood was lost from ulcerated areas at the anastomotic site (Owren[60] believes that this anemia is more likely due to the fact that under normal conditions the absorption of iron takes place in the duodenum and upper part of the jejunum, which is not permitted in the presence of abnormally rapid passage of ingested material through the upper part of the jejunum following gastric resection) The administration of ferrous salts orally would correct this iron deficiency anemia Next, Paulson and Harvey noted microcytosis of red blood cells, occurring within 1 to 2 years after operation, if the patients lived long enough this invariably was followed by anemia and, still later, by the development of megaloblasts in the bone marrow In patients in whom this macrocytic-megaloblastic type of anemia developed, beneficial response was obtained from parenteral therapy with vitamin B_{12} In this connection it is of interest that studies with cobalt-labeled B_{12} have shown that the function of the intrinsic factor of gastric juice has to do with promoting intestinal absorption of this vitamin [41]

Dietary disturbances and weight loss Following total gastric resection relatively large amounts of fat and nitrogen are lost in the stools, and this is the result of too frequent stools, if not actual diarrhea Everson[24] studied the effect of pancreatin n ducing fecal nitrogen and fecal fat loss lowing total gastrectomy in 12 dogs] creatin in adequate dosage was effecti appreciably reducing fecal nitrogen loss it did not restore the value to the lev normal dogs This substance had little e upon the fecal fat loss

Patients almost invariably lose subs tial amounts of weight following total moval of the stomach

Esophagoscopic observation of the es agoenteric anastomoses In view of the of the acid-pepsin factor in causing pe ulcer, the esophagoscopic observation Paulson[62] following total gastrectomy of interest He studied the appearanc the duodenum or jejunum (according to type of anastomosis used) in a serie more than 50 patients over a period seven years, and in none was marginal u or other peptic-like erosion encountere

Pathologic Physiology of the Small and Large Bowel

Survey of Normal Secretory, Absorpt and Motor Functions of the Small Bo

SECRETION AND ABSORPTION The secreti and other fluids that are poured into up small bowel are derived from the stoma pancreas, liver, and the intestinal glar In the duodenum are the distinctive Br ner's glands which secrete an alkaline ju rich in mucus, resembling that formed the structurally similar pyloric gland In experimental studies, stimulation of vagus nerve, injection of secretin, or p fusion of the duodenal lumen with a dil solution of hydrochloric acid stimulates secretion of these glands The *succus ente cus* (intestinal juice), then, arises fr the glands of the mucosa of the small bov and is an alkaline fluid containing muc and the enzymes enterokinase, amylase, a erepsin, the last being a mixture of seve specific enzymes which act principally a rapidly on the peptones and polypeptid converting them into amino acids Carb hydrates are acted upon by invertase (wh

converts cane sugar into glucose and fructose) and lactase (which converts lactose into galactose and glucose) Enterokinase, which is found mainly in duodenal juice, activates pancreatic trypsinogen Moreover, certain constituents of intestinal juice are said to increase the activity of pancreatic amylase and lipase Finally, there is secreted in the succus entericus a lipase which acts on fats and fatty acids. Mechanical stimulation of the intestinal mucous membrane increases the volume and total enzyme output intestinal obstruction or mucosal irritation may increase the volume of secretion. It will be recalled that pyloric obstruction results in an increased volume of gastric secretions

Absorption in the intestine Normally, almost complete absorption of the products of digestion and of other materials such as water salt, and vitamins occurs in the small intestine Apparently ileal absorption is even more important than jejunal absorption The mechanism of absorption of the different substances is quite complicated and is often very specific for the substance in question For example, although some sugar is absorbed from the intestine by simple diffusion a more important mechanism is that of active intervention of the living intestinal cells. The process involves phosphorylation of the sugar concerned, that is the union of the sugar with phosphate This occurs only with the "physiologic' hexoses—glucose, galactose, and fructose It does not occur with nonphysiologic hexoses such as mannose or the pentoses If the intestinal mucous membrane is destroyed, depressed by cooling to a low temperature or poisoned with phloridzin, 'active' absorption ceases and simple diffusion alone takes place The rate of absorption of a substance is related of course, to the state of the intestinal membrane at the time and upon the length of time that the substance is in contact with the membrane As is known, the local conditions necessary for the absorption of some substances such as certain vitamins, are highly specific Moreover in diarrhea or following massive resection of small bowel, the food substance may not remain in contact with intestinal absorptive surface long enough to permit proper absorption Certain endocrines (the thyroid, for example) affect the rate of glucose absorption from the bowel. Thyroxine stimulates the mucosa of the intestine to absorb more rapidly whereas glucose absorption may be depressed in adrenal cortical deficiency Again, the processes of absorption of other substances such as fats, proteins, and vitamins are equally specialized.

MOTILITY OF THE SMALL INTESTINE It would appear that material which has passed into the first portion of the duodenum is retained there until its acidity has been neutralized and is then carried rapidly into the jejunum. There is normally some anti peristalsis in the duodenal cap, but beyond this point slow peristaltic waves pass down the small intestine as a whole at intervals ranging from a few seconds to a few minutes By means of these waves the chyme is moved along so as to reach the cecum about 3½ hours after it leaves the stomach Segmentation movements of the small intestine occur, churning the chyme mixing it intimately with the digestive secretions, and exposing it to the absorptive surface of the mucosa. The rate of rhythmic segmentation of the intestine is progressively slower in successively lower levels of the bowel The segmentation or mixing movements are distinct from the longitudinal or propulsive movements.

The nervous control of the small intestine has not yet been clearly worked out. In general the vagus nerves increase the tone and motility of the small bowel, and the sympathetic nervous system has the opposite effect However, even after both sympathectomy and vagotomy the intrinsic innervation of the small bowel permits virtually normal peristalsis The normal intestinal movements would therefore appear to be controlled by local mechanical and chemical stimuli which affect the mucosa and cause contraction above and

relaxation below the site of stimulation, probably through the medium of Auerbach's plexus

It has been shown that when a length of intestine is reversed and anastomosed in the opposite direction, chyme may pass through it if the segment is not too long Moreover, it was shown by Wangensteen[87] that if progressive segments were reversed at different operations a surprisingly large amount of the small bowel might be reversed without lethal effects, though the passage of the material through it was slowed Nevertheless, it would appear that a segment not much longer than 12 in can be reversed at any given time This is an important consideration when doing the Roux "Y" type of anastomosis in establishing a "defunctionalized" loop, perhaps for common duct drainage Since in animal experiments it has been found that regurgitation of chyme can occur for a distance of 12 in, the optimum length for the antiperistaltic limb would appear to be at least 12 in

The effect of spinal anesthesia on intestinal motility varies somewhat in different subjects The sympathetic nerve supply is blocked by the spinal anesthesia, leaving the vagal action unopposed Dennis and his associates[16] performed vagotomy on 11 patients suffering from idiopathic ulcerative colitis By this procedure the time required for the passage of barium through the small intestine was increased from 3 5 hr preoperatively to 7 5 hr postoperatively, the passage of barium through the colon was increased from 3 1 hr preoperatively to 11 3 hr postoperatively It also seemed that vagotomy reduced the mucosal vascular response to emotional tension and relieved enteric spasm However, vagotomy as a means of managing chronic ulcerative colitis has not received wide acceptance

There is evidence also that hormones affect intestinal motility, as they do virtually every other function of the body The loose stools of thyrotoxicosis are well known, and the patient with hypothyroidism is apt to be constipated The injection of Pitressin causes gut contraction, and is of some aid in combating distention

Small Bowel Insufficiency

As with the lungs and kidneys, a considerable amount of the small intestine can be excised before digestion is appreciably affected Nevertheless, disability will occur if the amount of bowel resected at operation is great enough Extensive or "massive" resections are most often done for gangrene due to superior mesenteric arterial occlusion, volvulus, or, in the past, regional enteritis Occasionally, intestinal obstruction due to some inflammatory condition such as tuberculous peritonitis may require small bowel resection or by-passing of a type which results in small bowel insufficiency Absorptive insufficiency may also occur in the presence of a gastrojejunocolic fistula following gastric resection, whereby the food enters the stomach and then immediately enters the colon, by-passing the absorptive surface of the small bowel, this same physiologic defect is occasionally produced unwittingly by the surgeon, when at gastric resection the stomach is anastomosed to the ileum instead of to the jejunum in performing the gastroenterostomy The possibility of such an error should always be considered when the patient begins to have multiple loose or diarrheal stools immediately following surgery

As early as 1881 Kocher[45] removed 208 cm of small bowel, and in 1888 Senn[77] suggested, on the basis of experimental observations, that at least one-third to one-half of the small bowel must be resected to produce intestinal insufficiency In 1935 Haymond[33] collected and analyzed 257 cases, and a most important finding was that the amount of intestine which could be sacrificed without morbidity varied considerably in different patients This was due in part to different bowel dimensions Flint[28] emphasized that *the metabolic disturbances are proportional to the amount of intestine re-*

maining and not to the amount resected In a study of 160 adults, Bryant[6] showed that the length of the intestine varied from 10 ft. to 28 ft., 4 in Haymond concluded in his summary that 33 per cent of the small intestine can be removed without any serious metabolic alterations, but that if 50 per cent is resected one can expect definite instances of nutritional disturbance

Berman and his associates[3] reported a 6-year follow up study of a patient who had had extensive bowel resection for mesenteric thrombosis the cecum, ascending colon (10 cm.), and the small bowel (539 cm.), except for the duodenum and 45 7 cm of jejunum, were resected A macrocytic anemia developed very slowly, producing weakness, atropic glossitis and proctitis, and paresthesias of the hands and feet This responded to the administration of vitamin B_{12}

The study of another patient who had had a major portion of the small bowel resected was reported by Christensen and his associates.[9] The jejunum was divided approximately 2½ ft. from the duodenojejunal junction and the proximal jejunum was anastomosed to the transverse colon, the rest of the bowel being excised Twenty-one months later the postoperative diarrhea gradually lessened to only 4 movements per day He had not gained weight but neither had he lost weight, the value ranging from 120 to 125 lb

EFFECT OF SMALL BOWEL RESECTION ON NORMAL GROWTH To examine the effect of extensive small bowel resection upon the growth of young animals, Clatworthy and his associates[10] performed extensive small bowel resections in young dogs 40 to 80 per cent of the small intestine distal to the ligament of Treitz was resected in 19 puppies without impairment of their growth and development. The mechanism of compensation was considered to be due to an increase in absorptive surface and a decrease in the motility of the remaining small bowel It has been found that from 50 to 60 per cent of the intestine can be removed in children and still allow an individual to survive and to enjoy good health, however, if from 80 to 90 per cent of the bowel is removed, the outlook is poor

The principal metabolic disturbances that occur following massive bowel resection are due largely to diminished absorptive surface, with rapid transit of ingested food Intractable diarrhea results in marked weight loss due to excessive loss of fat and proteins in the stool Approximately 45 per cent of the ingested fats and 25 per cent of the ingested proteins may be lost in such cases, in contrast, carbohydrate absorption and utilization may be almost normal The fat loss is due less to defective breakdown of fatty acids (digestion) than to poor absorption Calcium loss may produce tetany, at times abetted by alkalosis Acidosis may develop

In addition to the above nutritional deficiencies, serious water and salt derangements must be anticipated and treated if they occur

ILEOPROCTOSTOMY It is at times desirable to resect the colon and then to re-establish bowel continuity by means of ileorectal anastomosis, thus preserving sphincter function I have done this operation in several patients for multiple polyposis of the colon, and have been particularly careful to follow the number and character of the bowel movements thereafter At first there may be from 10 to 15 loose stools per day, which are likely to result in at times severe perianal irritation and excoriation. However, the use of powders, zinc oxide ointment and other materials usually controls this discomfort fairly well and, as the weeks pass the number of stools gradually declines to from 4 to 6 per day and they become somewhat more firm in consistency The perianal irritation often disappears, and the individual can return to work without the constant apprehension that an abrupt rush of watery ileal material will result in social embarrassment. There is no doubt in my mind that most patients are better satisfied with the

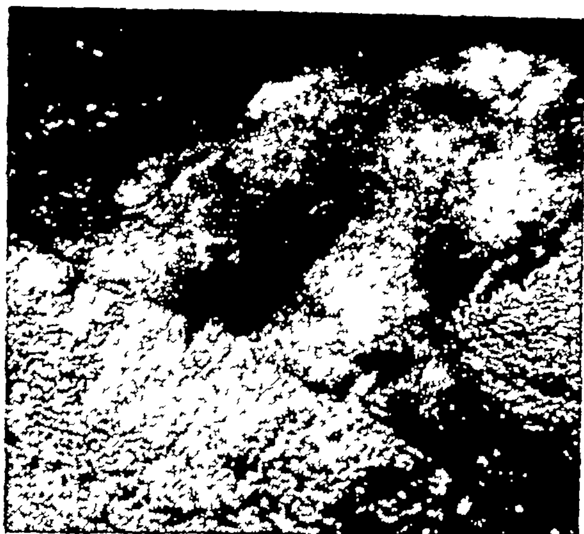


Fig 122 Small bowel fistula Note the excoriation and erosion of the surrounding skin, despite the use of aluminum paste The abdominal surface is best protected by constant and efficient suction at the opening Several liters may be collected in the trap bottle daily, and accurate fluid replacement is thus facilitated Small bowel loss is usually a balanced electrolyte loss, neither acidosis nor alkalosis is likely, but a low salt syndrome can readily develop

eventual result of ileoproctostomy than with ileostomy

Small Bowel Fistula (Fig. 122)

This lesion has been considered in the discussion of fluid therapy (p 73) and but a few points need repeating here The principal physiologic problem is that which results from water and salt loss, though gradually deteriorating nutritional status and infection eventually contribute significantly As many as 6 L may be lost from the drainage tract of a high jejunal fistula over a period of 24 hr The salt loss is a more or less balanced one, however, and neither acidosis nor alkalosis is typically encountered In time the salt loss may exceed the water loss, resulting in hypotonicity of the extracellular fluid Potassium and even calcium deficits may eventually develop

The *prognosis* of small bowel fistulas is generally good, if hydration and a degree of nutrition are maintained, time is gained for the fistula to close, usually in a week or two Occasionally, a tube for feeding can be got past a high intestinal defect, which is most helpful If the lesion does not close, the increasing tendency is to reoperate, attacki the fistula directly by resection of the i volved bowel, or by anastomosing arou it That a fistula actually exists can be e tablished by having the patient swallow i digo carmine or methylene blue, the level the defect can be established by roentg examination following ingestion of bariu Fistulas of the jejunum or ileum are mo readily repaired surgically than are du denal fistulas While it has been shown th experimental duodenal side fistulas in do can be closed successfully in a great m jority of the animals,[81] in patients it will times be preferable to perform a subtot gastric resection as management for a pe sistent duodenal side fistula, draining t duodenal area widely This converts a si fistula to the less serious end fistula, gastr secretions are no longer lost, and the patie can be fed If a duodenal fistula follow gastric resection, the underlying cause ma be obstruction of the proximal loop

A jejunal fistula may be by-passed b making an incision at a distance from it opening on the abdominal wall, avoiding th infected area Following entero-enterostom the flow to the outside is usually much di minished, permitting rapid improvement i the patient's general condition The fistulou loop can be resected later as an elective pro cedure To aid in identification of the prox imal and distal bowel at operation, one ca pass a Miller-Abbot tube through the nos preoperatively and allow it to progress unti it has reached the site of the fistula If th fistulous loop of bowel is superficial and th wound is partially separated, the tip of th Miller-Abbott tube may actually protrud onto the abdominal wall If the tube reache the fistula preoperatively, one can assume at operation that any loop of bowel that contains Miller-Abbott tube is proximal bowel and that any loop of bowel that does not contain Miller-Abbott tube is distal bowel, the anastomosis is performed accordingly, as noted elsewhere

Ileal fistulas are not usually associated with unmanageable fluid and nutritional

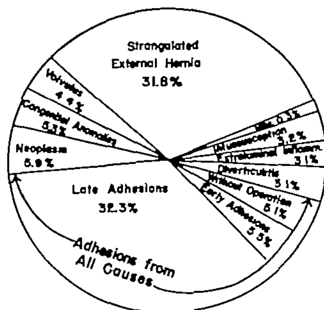
losses and thus a longer period of conserva tive management is feasible

Intestinal Obstruction

The *etiology* of intestinal obstruction in 1287 admissions, including both children and adults, is shown in Figure 123

PATHOGENESIS AND PHYSIOLOGIC CHANGES Not only the clinical picture but also the physiologic derangements encountered will depend upon the level and the mechanism of the obstruction. For example, chronic in complete colon obstruction may result in weight loss and anemia before colic finally impels the patient to seek medical advice. Yet if the incomplete or partial obstruction suddenly becomes complete in the presence of a competent ileocecal valve, abdominal pain develops quickly due to what amounts to a closed loop obstruction and, should sur gical relief not be forthcoming gangrene of the bowel wall with perforation may prove fatal A somewhat similar problem presents with low small bowel obstruction In both instances fluid loss to the outside by vomit ing is not usually excessive but the threat of ischemic necrosis of the bowel wall is great. In contrast high small bowel obstruc tion results in prompt vomiting and marked fluid loss to the outside however since the obstructed bowel is decompressed by vomit-ing the danger of gangrene from distention is much less Basically, then death in low obstruction is more commonly due to stran gulation or ischemic necrosis of the wall of the distended bowel while death in un treated high small bowel obstruction is apt to be due to fluid loss Of course, these pic tures overlap to varying degrees but it is far safer to treat high obstruction conserva tively than low obstruction The surgical mortality in simple (nonstrangulating) ob-struction is less than 10 per cent but in pa tients who have necrotic bowel that must be resected the mortality is approximately 25 per cent

A closed loop obstruction is quite serious no matter what the level, since even if it is high the loop cannot be decompressed by regurgitation



CAUSES OF INTESTINAL OBSTRUCTION IN 1,287 ADMISSIONS

Fig 123 In large series of cases from different clinics the percentage of cases falling into each of the categories is remarkably similar to the figures given above (From BRAMLITT E E HARDY J D., AND WILSON H Intestinal Obstruction. II Analy sis of 1287 admissions over a ten year period Am Surgeon **21** : 1001 1955)

SOURCE OF THE FLUID AND GAS IN SMALL BOWEL OBSTRUCTION In Figure 22 it is shown that the volume of secretions normally poured into the upper intestine—the succus entericus bile pancreatic juice, gastric juice, and saliva—amounts to more than 7 L per day In addition, obstruction of a portion of the alimentary tract may lead to an in creased rate of secretion as in pyloric and (probably) small bowel obstruction. For ex ample in 1922 the Dragstedts[19] observed an increased secretion of gastric juice, pan creatic juice and bile following intravenous injection of obstructed loop content from other dogs They postulated that distention of the obstructed loop produced a secreta gogue Finally, a transudate from the blood increases the fluid in the bowel lumen, as increasing intraluminal pressure compresses the venous outflow while arterial inflow con tinues Eventually not only transudate but

also considerable plasma and blood may be lost in this way

The *gas* which distends the bowel in obstruction is derived from three sources [87] By far the greatest portion (70 per cent) is derived from swallowed air The importance of this source was demonstrated by producing small bowel obstruction in the presence of an esophageal fistula Distention was markedly less and the animals survived longer Thus, the nasogastric tube not only aspirates gas already present but guards against the entrance of further air into the bowel Less important volumes of intestinal gas are derived from gases contained in the blood (20 per cent) and from bacterial metabolism in the intestine (10 per cent)

INTRALUMINAL PRESSURE IN STRANGULATION OBSTRUCTION To comprehend the mechanical factors in the genesis of strangulation obstruction, the rôle of intraluminal pressure must be understood As a point of departure, let it be noted that many barium enemas are performed with a pressure that is higher than that found in intestinal obstruction with strangulation Why, then, does not the barium enema perforate the bowel, except in the very occasional case? It does not do so because the high pressure transmitted to the colon wall is not long sustained Therefore, not only is the absolute *level* of the pressure important, but the *duration* over which the pressure is maintained is also quite important A moderately increased pressure that persists over a prolonged period may prove more disastrous than a markedly elevated pressure that persists only a short while The mechanism of bowel perforation in the presence of long continued distention is not unlike that of skin necrosis overlying a bony prominence in the debilitated patient Once the skin has become slick and shiny and erythematous, very little additional pressure is required to produce a decubitus ulcer or "pressure sore" *Distention of the bowel must not be allowed to persist too long, and this is the major factor which limits the time that can safely be devoted to the conservative manageme[nt] of obstruction*

In 1907, Van Zwalenburg[84] studied [the] effect of distention of the bowel upon blo[od] flow through the wall It was noted that ca[p]illary stasis occurred at 30 mm. Hg pressu[re], venous stasis at 60 mm, partial arterial [ar]rest at 90 mm, and finally complete arr[est] of the circulation at 130 mm In 1929 Dra[g]stedt, Lang, and Millet[18] made similar o[b]servations at different levels of the alime[n]tary canal and found that the circulati[on] of the duodenum was more profoundly a[f]fected by increased intraluminal pressu[re] than was that of any other portion of t[he] bowel As might be expected, the burstin[g] tension of experimentally obstructed loo[ps] is less than that for normal bowel

Wangensteen[87] showed that acute rap[id] overdistention of the gut results in elonga[tion] of the bowel, as measured in excis[ed] segments and *in vivo* However, when t[he] bowel has been exposed to sustained diste[n]tion over a period of hours, contraction [of] the longitudinal muscle may result in short[en]ing of the bowel length, though in chroni[c] obstruction lengthening of the bowel is n[ot] unusual Nemir and his associates[57] reporte[d] much lengthening of experimentally stran[gulated] intestinal segments in dogs

PRESSURE MEASUREMENTS A considerabl[e] number of measurements of intra-enter[ic] pressures in the obstructed small and larg[e] bowel were made by Wangensteen [87] In ex[perimental] animals the pressure in the ob[structed] small bowel was an average sus[tained] value of 9 cm H_2O, with a range o[f] from 4 to 19 cm In clinical measurements the sustained pressures in four cases of clinical obstruction of mechanical origin of from 48 to 96 hr duration varied from 4 to 14 cm H_2O, with occasional pressures of from 20 t[o] 30 cm H_2O during peristaltic activity Pressures were also obtained at operation when colostomy was performed for the relief of distention in five cases of acute colonic obstruction due to malignancy. The sustained pressures varied in these five cases from 12

to 52 cm H_2O In four of the cases pressures above 23 cm. H_2O were recorded, much higher values than were observed in small bowel *obstruction—for colon obstruction* is likely to represent closed loop obstruction, with gas continuing to enter through the ileocecal valve but prevented from escaping by the same avenue in approximately 60 per cent of cases The duration of obstruction in these four cases ranged from 3 to 10 days

Thus, in large bowel obstruction intraluminal pressures of from 10 to 25 cm. H_2O are the usual findings, and are observed even when a tube is in the duodenum with continuous aspiration prior to operation This again underscores the difference between small bowel obstruction and obstruction of the colon in the presence of a competent ileocecal valve The relatively high pressures developed in colon obstruction shorten the time that conservative management may be tried

LOW SMALL BOWEL OBSTRUCTION AND COLON OBSTRUCTION—CHANGES IN THE BOWEL WALL. The infusion of large amounts of saline solution which is so effective in improving the over all condition of the patient with simple high intestinal obstruction, is not nearly so effective in achieving general improvement in the status of the patient who has low intestinal obstruction Low obstruction therefore produces a more sinister pathologic situation, and the results of therapy are often disappointing In the following paragraphs obstruction of the colon will be considered along with obstruction of the low small bowel though it is to be remembered that obstruction of the colon frequently represents a closed loop obstruction because of the competency of the ileocecal valve in somewhat more than one-half of the patients

Prolonged distention impairs the integrity of the bowel wall. In studies of the effect of sustained pressures upon the anatomy viability and permeability *of the bowel* wall Wangensteen[37] found that poisonous substances introduced into the bowel did not pass through the bowel wall into the peritoneal cavity and become absorbed so long as the gut wall was viable Whereas an intra-enteric pressure of 10 cm continuously sustained for 27 or 28 hr caused petechial hemorrhage in the bowel wall, it was still viable and not abnormally permeable Similarly an intra-enteric pressure of 20 cm H_2O sustained for from 10 to 22 hr caused congestion of the bowel, but it was still viable However, pressures of 20 cm maintained for from 28 to 32 hr caused necrotic patches to appear in the gut, the bowel was no longer viable and permitted the diffusion of the potassium ferrocyanide through its wall Pressures of 40 cm H_2O were tolerated as long as 11 hr but when continued thereafter necrosis of the gut wall with abnormal transperitoneal diffusion occurred. The obstructed bowel did not absorb water normally An 18 in loop of lower ileum absorbed in an hour 87 per cent of the water necessary to fill it, whereas in similar but previously obstructed loops only 9 per cent was absorbed This accounts for the fact that large amounts of fluid may be trapped in clinically obstructed bowel, this fluid is not available to the circulation and extracellular volume because it is poorly reabsorbed.

BLOOD LOSS IN STRANGULATION OBSTRUCTION One of the most commonly observed findings when the peritoneum is opened in the presence of a strangulated loop of bowel is the dark bloody fluid, the color of which is derived from hemoglobin. There is often considerable hemorrhage into the bowel lumen, and this may later cross the impaired wall and enter the peritoneal cavity The important clinical point here is that blood transfusion is strongly indicated in the presence of strangulation obstruction

CAUSE OF DEATH IN STRANGULATION OBSTRUCTION There continues to be much debate regarding the ultimate cause of death *in strangulation* obstruction but virtually everyone agrees that, whatever the cause it

comes into effect and produces clinical signs only after the viability of the intestinal wall has been impaired Therefore, the serious consequences of bowel necrosis appear to be due to the passage of some substance from the intestinal lumen into the peritoneal cavity and its subsequent absorption into the blood stream—with the profound toxic effects which include prostration and irreversible shock (*see* Case Study, p 1) This substance may represent bacterial toxins *per se*, perhaps from clostridia, or it may be due to substances which are formed by chemical processes within the bowel lumen but which are not primarily bacterial toxins Nemir and his associates[57] concluded that the offending substance may be ferritin, but probably a majority of workers are inclined to favor the bacterial toxin hypothesis In any event, the dark fluid in the peritoneal cavity in experimental obstruction is highly lethal for other dogs when given intraperitoneally or intravenously.

DIAGNOSIS OF INTESTINAL OBSTRUCTION The presence and possible etiology of intestinal obstruction are usually established by a careful history and physical examination, and are confirmed by appropriate roentgenograms Vomiting that is associated with cramping or colicky abdominal pain and failure to pass gas, particularly if distention and borborygmi are present, should always render bowel obstruction a leading diagnostic possibility The history of a previous operation, or the presence of a hernia, or the history of weight loss suggesting a malignancy are all important points in the cause and probable level of obstruction Yet, even though the diagnosis of intestinal obstruction might appear simple in the telling, the failure to appreciate the problem promptly and to act appropriately still results in the loss of a large number of lives each year The fact is, intestinal obstruction can present extremely difficult diagnostic and therapeutic problems, and few other conditions require greater clinical judgment for consistently successful management

PRINCIPLES OF MANAGEMENT IN OBSTRUCTION (FIG 124) *General considerations* It is a good plan to hospitalize immediately any patient who exhibits signs and symptoms which suggest intestinal obstruction, since only if continuous close observation is maintained can impending gangrene be anticipated and surgery performed promptly In general, patients with high small bowel obstruction that is likely due to postoperative adhesions deserve a reasonable period of conservative management with tube suction, intravenous fluids, and, if desired, antibiotics The reason for choosing conservative management in these patients is not only that the obstruction may subside but also that operation might result in even more adhesions. Needless to say, closed loop obstruction should not be treated conservatively if it is complete and is recognized High small bowel obstruction presents, as noted, chiefly the problem of fluid and nutritional maintenance, since decompression is achieved by vomiting or tube suction, strangulation is unlikely

Low small bowel obstruction, on the other hand, is managed conservatively at considerable risk unless a long tube passes down the bowel promptly to effect decompression If pain is not soon relieved, if the pulse rate remains above 100, if the temperature begins to rise, if there is a tender mass, if signs of peritoneal irritation are developing and leukocytosis is increasing, if the blood pressure declines, or if the patient's general appearance is unsatisfactory—if any or all of these circumstances develop—operation should probably be performed without further delay To repeat, the mortality increases sharply when gangrene necessitates bowel resection Incidentally, should the pain cease but the patient's general condition be worse, bowel gangrene should be suspected As successful suction and intravenous fluid therapy are initiated, a previously rapid pulse rate should slow, if it does not, one should be alert to possible strangulation

Colon obstruction, if complete, demands immediate operation

Continuous suction Regardless of whether operative intervention or conservative therapy is to be utilized initially, the upper

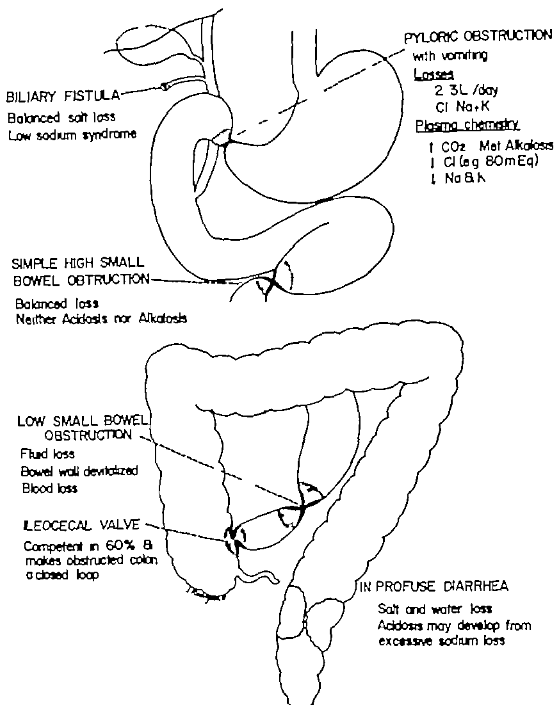


Fig 124 This diagram emphasizes the fluid losses in alimentary obstruction at successive levels, with biliary fistula and diarrhea included for comparison. The hazard in pyloric or high small bowel obstruction is that of fluid loss and shock Fluid (and blood) losses are also important in low small bowel obstruction, but here the sinister effects of strangulation obstruction with devitalization of the bowel wall and peritoneal contamination predominate Thus, with adequate fluid replacement one can safely temporize with high obstruction, but strangulation is an ever present danger in low obstruction—regardless of fluid requirements. Small bowel obstruction only rarely produces marked alkalosis or acidosis

reaches of the gastrointestinal tract should be promptly decompressed by continuous suction. In the event conservative therapy is used the suction will minimize vomiting and will diminish distention of the proximal bowel If surgery is contemplated suction should still be employed preoperatively, for it will remove the major portion of the fluid

from the stomach and duodenum and will thus diminish the possibility of aspiration by the patient during anesthesia—in addition to relieving the deleterious effects of the gastric distention which may have reflex effects upon the blood pressure as well as compression effects upon the liver and vena cava

In 1934 the Miller-Abbott tube[55] was described for decompression of the lower reaches of the gastrointestinal tract Essentially, it was shown that, by inflation of a balloon after the tip of the tube was in the duodenum, peristalsis would advance this balloon (and with it the tube) and that the tip often would progress to the anus As the tube was only about 11 ft in length, it was apparent that the bowel had been telescoped or "reefed" on the tube Since to withdraw the tube from the nose under such circumstances subjected the bowel to considerable traction with the possibility of intussusception (not to mention esthetic considerations) it was found expedient to remove the Y-shaped proximal tip at the nose and to pull the tube through per anus Obviously the tube should not be released at the nose until it has been secured below, or else laparotomy might conceivably be required to retrieve the tube Incidentally, one may take advantage of the decompression and reefing effect of the long tube to minimize bowel interference during resection of the abdominal aorta.

There has been much argument concerning whether or not a simple Levin tube, introduced into the stomach and if possible into the duodenum, is as effective in decompressing the gastrointestinal tract as is one of the various types of long tubes We believe that it is preferable, even when operation is to be performed, to introduce a long tube initially While the tube may not have left the stomach at the time of laparotomy, the surgeon can push the tip of the tube through the pylorus and duodenum, much after the fashion of the reinsertion of a pajama string attached to a safety pin by reefing the cloth upon the safety pin in successive advances Once the tube is in the jejunum the balloon may be inflated, permitting the tube to advance postoperatively, decompressing as it goes For, even if the obstruction has been relieved by operation, it is of considerable value to decompress the bowel as rapidly as possible, and the long tube more speedily accomplishes this.

At times the large volume of secretions which flow into the upper gastrointestinal tract may cause pooling in the stomach after the long tube has passed well down into the intestine, too far to empty the atonic upper bowel Under these circumstances it may be desirable to insert a Levin tube through the other nostril and to decompress the stomach, either continuously or intermittently

Were it not for the fact that one can reach the lower bowel with the long tube, it would probably be preferable to insert a short Levin tube into the stomach, since gastric aspiration *per se* is more effectively accomplished with one of the short tubes than with the long tubes, owing to the greater friction along the latter and to the greater likelihood that the smaller lumen of the long tube will become plugged with mucus and other detritus

Unfortunately, it is often in the patient who is in the greatest need of effective decompression that the most difficulty is encountered in passing the long tube into the small bowel In the early days of the Miller-Abbott tube usage in Philadelphia, one usually employed a long wire stylet to propel the tip of the thus stiffened tube into the duodenum, using fluoroscopic guidance The balloon was then inflated and the wire stylet withdrawn Even with the stylet, however, failures were common in markedly distended patients, and at the present time we no longer attempt to use the stylet If the tube cannot be maneuvered into the small bowel in a reasonable period of time and adequate decompression achieved, we operate upon the patient

How long should conservative management be continued? It is always a matter of

fine clinical judgment as to how long to continue conservative therapy, and no single rule can be laid down. However, three guides may be mentioned. First, the abdominal distention should begin to subside and the pain should be relieved. Second, serial roentgenograms of the abdomen should show a decline in the degree of bowel distention and certainly should not show progressive distention. Third, the general condition of the patient and his response to the over all plan of conservative management must be satisfactory: this includes his general appearance, pulse rate, blood pressure, abdominal tenderness and rigidity, absence of persistently tender masses, character of suction material, and whether or not passage of flatus resumes. *The commonest error in the management of intestinal obstruction consists of continuing conservative management too long and permitting gangrene to occur.*

Fluid replacement. The physiologic principles of fluid replacement therapy have been outlined in Chapter 2, and only a few points need be repeated here. While it has been emphasized that large amounts of salt-containing fluid may be lost to the outside by vomiting in high obstruction, large amounts of salt containing fluid are lost *into* the bowel in low small bowel obstruction (Fig. 124). This loss into the bowel, which cannot absorb fluid at a normal rate, may just as effectively dehydrate the patient as if the fluid had been lost by vomiting. Adequate fluid replacement is necessary in all types of obstruction.

To review, the precise therapy required in any given instance of water and salt depletion will depend upon the character of the losses. It has been seen that in pyloric obstruction a preponderant loss of chloride and potassium usually results in hypochloremia and in metabolic alkalosis that is reflected in an increase in the carbon dioxide combining power of the extracellular fluid (plasma). As one proceeds down the small bowel, however, the loss usually becomes a more balanced one, and neither acidosis nor alkalosis of a serious degree is commonly encountered in small bowel obstruction. The mainstay of therapy will be isotonic sodium chloride solution, or a balanced solution comprised of one-third M/6 sodium bicarbonate solution and two thirds isotonic sodium chloride solution. There may have been a preponderant salt loss, as compared with water loss, and initially it may be advisable to give hypertonic saline solution (500 ml to 1 L of 3 per cent) to overcome the osmolar deficit. This may be followed with a volume of isotonic saline in glucose solution equal to 8 per cent of the patient's body weight, if signs of marked dehydration are present. Since the markedly dehydrated individual has frequently lost from 8 to 10 per cent of his body weight as water, the replacement of 8 per cent of 70 kg results in a volume of fluid of approximately 5600 ml. or roughly 6 L. This is the amount of fluid which is required to replace the deficit existing at the time of admission. But if 2 L. of fluid are aspirated from the stomach during the first hour or so of suction, then one must add this volume as well as any continuing losses in the form of urine, further suction material and sweating to the initial requirement if normal hydration of the individual is to be regained. However, one will not wish to infuse 8 L. of fluid over a very short period of time, and this points up the fact that fluid losses which have occurred over a period of several days should not—cannot—be corrected precisely in 2 or 3 hr. A definite plan of orderly but expeditious restoration of the fluid deficits should be initiated, with probably no more than 5 L. of fluid being given in the first 12 hr. At the end of each 12 hr. or less the total picture is re-evaluated and over all therapy altered according to the findings.

If emergency operation is indicated, we usually give from 2 to 3 L. of saline solution, often with an infusion of 500 ml. of whole blood, and continue fluid therapy after the surgery. At operation as much blood is used as is required to maintain a satisfactory blood pressure, and liberal transfusion is an important aspect of treatment. These indi

viduals often come to operation with a blood volume which may be from 1 to 1 5 liters low because of dehydration, perhaps from anemia due to a malignant tumor and from loss of blood into the bowel wall, the intestinal lumen and, in severe cases, into the peritoneal cavity The use of adequate amounts of blood will materially diminish the operative mortality in patients coming to surgery for intestinal obstruction

Antibiotics Although antibiotics have not greatly diminished the over-all mortality rate in intestinal obstruction, it was shown by Cohn[12] and by Poth[67] that a loop of bowel whose blood supply had been impaired would often survive without perforation in experimental strangulation if large amounts of antibiotics were given, in control animals the rate of perforation with peritonitis and death was much higher Therefore, regardless of the statistical analyses, there would appear to be sound indication for giving liberal amounts of antibiotics to some patients with intestinal obstruction, if for no other reason than to diminish the severity of peritonitis should the viability of the intestinal wall become impaired during conservative management Penicillin and streptomycin, in combination, constitute satisfactory therapy for this purpose

OPERATIVE INTERVENTION Operation is usually resorted to after conservative management has been considered and perhaps given a trial, but has not been sufficiently effective

Anesthesia and incision The anesthetic used is less important than the competence of the anesthetist using it If a general anesthetic is to be employed, an endotracheal tube should be inserted to prevent pulmonary aspiration should the patient vomit beneath the mask Spinal anesthesia is satisfactory, and local anesthesia can be used in the occasional critically ill patient

By and large, either a suitably placed transverse or a vertical incision will afford satisfactory exposure, though an adequate paramedian incision is our usual choice. Naturally, if obstruction is due to a hernia the appropriate herniorrhaphy incision is made Once the peritoneum is incisec color and the odor of free fluid are n Dark bloody fluid indicates strangula and a foul odor usually indicates perite soiling Where possible, it is advisabl identify collapsed bowel and to follow it ward to the level of obstruction, rather to deliver the entire obstructed bowel the abdominal wall and proceed downw Nevertheless, in some adults and in m infants evisceration is required.

The management of distention at op tion One of the most vexing technical p lems at operation upon patients with in tinal obstruction may prove to be tha returning the distended bowel to the per neal cavity at the time of closure This c stitutes a further argument against need complete evisceration, since distention of eviscerated loops often increases with t and it may be most difficult to return th distended loops of bowel to the peritor cavity later

We have experienced no complicati from aspirating and decompressing c tended bowel by various means, and c tainly closure is facilitated, not to ment the general desirability of diminishing f ther ischemia of the bowel wall

Bowel that is not clearly viable afte suitable period of observation should be sected, usually with end-to-end anastomo In contrast to the management of colon c struction with a colostomy, small bowel co tinuity should almost always be re-esta lished following resection. To construct double-barreled small bowel fistula produ a serious problem Side-to-side anastomos are usually satisfactory, but rarely the bli cul-de-sac may enlarge (Fig 125)

Operations for colon obstruction In mo instances colon obstruction is best manag in the emergency by a decompressing proc dure, deferring resection of a malignant l sion until later Of course, volvulus m force resection and anastomosis, but he too, if reduction of the volvulus results in return of satisfactory bowel color, resectio is best postponed until a later date The re

son for this is that the greatly distended and hence thinned colon wall is easily torn and, should leakage at a line of anastomosis occur following primary resection, death would usually ensue Again, the seriousness of peritoneal contamination by alimentary contents increases progressively from the stomach to the anus It was seen in Chapter 5 that acidity is inimical to bacterial growth, and gastric acidity is no exception, gastric contents have a mild bacterial flora.

Therefore, for lesions beyond the cecum a cecostomy or, much better, a decompressing colostomy is performed as a primary procedure. If the obstruction is in the cecum, then the distal colon has not been distended, under these circumstances the right colon may be resected with end to-end or end to-side ileotransverse colostomy However, if the patient s condition is poor a simple bypassing ileocolostomy should be performed initially leaving resection of the lesion for a second operation If a colostomy is, for various reasons, to be a permanent one, the more distal it is located the more easily can the less liquid movements be managed by the patient and his relatives

Use of long tube as a postoperative splint It may be necessary at times to operate in the subacute postoperative periods for adhesions both fibrinous and fibrous Yet there is no assurance that they may not re-form and require a third operation. Under these conditions a useful maneuver consists of advancing a Miller Abbott tube through the duodenum and into the upper jejunum manually while the abdomen is open. The balloon is then inflated and the tip of the tube is allowed to progress rapidly to the sigmoid colon while the bowel is not obstructed. The balloon is then deflated and the tube left undisturbed until the patient is ambulatory having bowel movements and eating a full diet. By this time the loops of bowel may have become encased in new fibrinous adhesions but sharp kinking has been prevented and a patent bowel lumen has been maintained. The Y-connection at the nose is then removed and the tube drawn

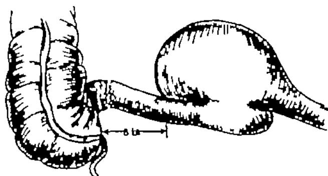


Fig 1?5 Enlargement of the blind stump in side-to-side anastomosis (From Clawson D K Side-to-side intestinal anastomosis complicated by ulceration, dilatation and anemia A physiologically unsound procedure Surgery 34: 254 1953) In our experience this condition has not constituted a common complication. While end-to-end anastomoses are preferred, side-to-side procedures are usually satisfactory

through from below As noted elsewhere, the entire Miller Abbott tube approximately 11 ft. in length may readily traverse the bowel from the nose to the anus, since the bowel "gathers" upon it. Again, the lower end of the tube must be secured before it is freed at the nose While such a warning might appear superfluous the writer was once associated with just such a circumstance fortunately, it was possible with a sigmoidoscope to reach the distal tip of the tube and to pull it on through without having to resort to operation.

Paralytic Ileus

In addition to *simple mechanical obstruction* (in which the primary defect is fluid loss) and *strangulating obstruction* (in which the bowel blood supply is compromised and may lead to gangrene), there is the third common cause of intestinal propulsive dysfunction, *adynamic ("afunctional or paralytic") ileus* In this condition no mechanical obstruction exists but effective motor activity of the bowel is lost. This is a major cause of morbidity on surgical wards, and it has a wide spectrum of causes. Operations upon the bowel itself or within the abdomen produce a majority of the instances encountered, but intracranial intrathoracic, or other procedures also result in paralytic ileus In fact bowel function is ab

normal in stress of many types Peritonitis, renal calculus, uremia, retroperitoneal hemorrhage, spinal injury, and hypopotassemia represent additional circumstances under which paralytic ileus may develop

The *management* of ileus is frequently unsatisfactory, until the precipitating condition has run its course Nasogastric suction is used, and oral intake avoided A rectal tube may facilitate the passage of colon gas, assisted with indeterminate success by injections of Pitressin, Prostigmin, or enemas *Potassium deficits should be corrected* Bowel perforation due to distention associated with ileus is rare

Regional Enteritis (Ileitis, Crohn's Disease)

In 1932 Crohn, Ginzburg, and Oppenheimer[13] described a granulomatous lesion of the terminal ileum which was given the name terminal ileitis However, it has since been appreciated that this subacute or chronic cicatrizing inflammatory process may involve almost any segment of the small bowel, often at multiple sites with uninvolved segments of bowel between The name now most used is regional enteritis (Fig 126)

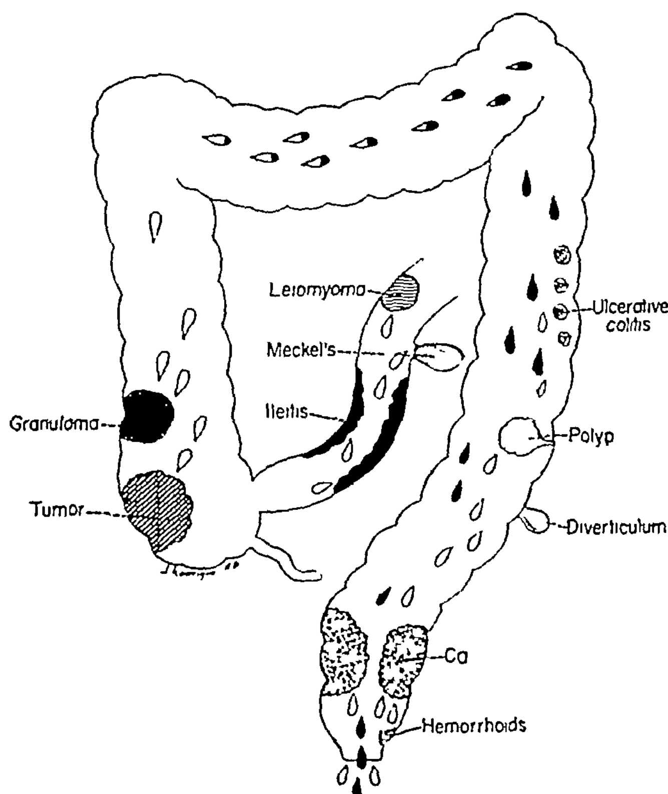


Fig 126 The passage of bright blood usually indicates a lesion in the lower small bowel or colon Nevertheless, intestinal motility varies greatly in different subjects, by injecting blood into the duodenum by tube it has been demonstrated that in some subjects the blood can appear in the rectum within minutes, virtually unchanged Too, bowel length varies from one person to another Even vigorous duodenal bleeding may fail to regurgitate into the stomach

Operation is required for several complications due to this process, the etiology of which is unknown First, the acute process may simulate acute appendicitis, and at surgery a fiery red, granular, edematous, and friable appearance of the terminal ileum and, often, the cecum is encountered If the base of the appendix is involved it is usually best not to perform appendectomy, lest a fecal fistula result Under these circumstances we usually do no further surgery, *but close the abdomen and adopt a conservative program*—for unquestionably many instances of the acute disease subside without further difficulty Second, the subacute condition may be associated with abdominal pain and tenderness, diarrhea, weight loss, leukocytosis, anemia, and fever, often with the formation of enteric fistulas Roentgen barium study may reveal multiple sites of abnormal mucosal patterns, with or without narrowing of the bowel lumen for considerable distances ("string sign") Operation at this stage of the disease reveals much evidence of inflammation, but it is less acute Characteristic of this and later stages is a tendency for the mesentery to become quite thickened and to tend to extend toward the antimesenteric border on either side—that is, to encircle the bowel To resect all the obviously diseased small bowel in extensive cases may be to risk intestinal insufficiency, or at least loose stools Therefore, *operation is best avoided at this stage, where possible* Finally, the third or quiescent stage of the disease may bring the patient to laparotomy for small bowel obstruction due to fibrosing stenosis The obstruction may at first seem to have occurred quite suddenly and without antecedent disease—there being no hernia, previous *operation, or suggestive evidence* of tumor in the adult patient Nevertheless

a careful history will often reveal that the patient once had bouts of unexplained diarrhea, perhaps years before, and that in recent months he has had "gas pains" or cramps upon occasion. What happened, of course, was that a chronically stenosed portion of the small bowel, through which the liquid contents of the small bowel could still pass, had suddenly become completely blocked, perhaps by undigested food particles.

Microscopically, the picture is that of a chronic granuloma which contains giant cells and in some respects resembles tuberculosis. However, again, no definite etiologic agent has ever been proved. Psychogenic factors appear to be far less important in this disease than in ulcerative colitis. Furthermore the beneficial effects of ACTH and cortisone that are often realized in ulcerative colitis are virtually absent in regional enteritis.

The *prognosis* of regional enteritis can be most unsatisfactory. The patient whose acute disease was disclosed unexpectedly at laparotomy performed for "appendicitis" may anticipate remission with some confidence. Where the subacute disease is limited to a short or relatively short total length of bowel, resection of this bowel may at times be justified. And yet, any resection should be performed with the full realization that subsequent involvement of remaining bowel may produce complications that could impel further resection in the future. Certainly one is well advised to be most conservative in resecting bowel for this condition, operating chiefly for the *complications* of obstruction and fistula formation. In time, the inflammatory process tends to subside and a permanent remission may be hoped for. Meanwhile, supportive measures such as transfusion, aggressive alimentation, indicated antibiotics, and continuous encouragement are imperative. Antispasmodics are of assistance in the management of some individuals. Cortisone therapy has not been notably beneficial, and opiates are best avoided, as they are best avoided in most chronic diseases.

Mesenteric Vascular Occlusion

Occlusion of the superior mesenteric artery usually results in gangrene extending from the first portion of the jejunum to the transverse colon approximately. The source of the arterial embolus may be a mural thrombus secondary to myocardial infarction, but more often it is from the left atrium in patients with atrial fibrillation. Local thrombosis of the artery may also occur secondary to thromboangiitis obliterans, polycythemia vera, or atheromatous changes.

Two patients may be cited to illustrate thrombosis, since embolism is so much more common that most are familiar with it. The first patient was a middle-aged white woman who was admitted with moderate abdominal distention and marked tenderness plus *mental disorientation*. It was considered by several examiners that the most likely diagnosis, in this woman who had been sick for several days, was peritonitis and beginning abscess formation secondary to a perforated appendix. The writer concurred. Conservative management was begun with antibiotics, nasogastric suction, and intravenous fluids. Transfusion was not given because the admission hemoglobin level was 17 gm. and the hematocrit 55 per cent. Since she did not exhibit an apparent degree of dehydration that might have produced this elevated hematocrit level, the hematologists were requested to consider the possibility of polycythemia vera, which was confirmed. However, at the end of 24 hr. of conservative therapy she had not improved, and it was decided to explore the abdomen—the mental condition remaining unchanged. At laparotomy a loop of gangrenous bowel was successfully resected. Pathologic examination of the specimen revealed widespread acute, subacute, and chronic thromboses of the smaller mesenteric vessels. She died several months later, having never exhibited normal mentality. Autopsy revealed extensive thrombosis in the vessels of the remaining bowel, but *the main* superior mesenteric artery and sufficient *smaller vessels* remained patent to allow

continued bowel viability Moreover, extensive thromboses were found in other organs, including the brain The patient's husband recalled that for the past several years she had had intermittent episodes of abdominal pain, and there had been the progressive mental deterioration

The second patient, a white man in his fifties, had undergone successful and uneventful resection of the aorta from just below the renal arteries to the femoral arteries for chronic thrombotic occlusion All was well until 6 a m on the morning following surgery when he was seized with abdominal pain At first there was no change in the vital signs, but after an hour or so the blood pressure fell and the pulse rate increased Naturally, some complication of the anastomosis or of the plastic prosthesis was considered the most likely source of the difficulty and, while the femoral pulses remained good and there was no definite evidence of blood loss, the abdomen was explored in the early afternoon Necrotic bowel was evident as the peritoneum was reopened, and it was soon apparent from the distribution of the gangrene (duodenum to transverse colon) that the superior mesenteric artery was occluded This bowel was resected, the first 3 in of jejunum being anastomosed end-to-end to colon The patient died within 24 hr from the irreversible shock that had been present at the time of operation due to the gangrenous bowel with passage of toxic materials through its wall Even so, he could not have survived in any event, because inadequate gut absorptive surface remained At autopsy it was found that thrombosis had begun on the site of an atheromatous "ulcer," and had gradually occluded the superior mesenteric artery at its origin The vascular clamp had been placed across the aorta below this level, but retraction or other manipulation may have produced structural change in the calcified intima, with clotting and fatal issue in what had been a straightforward elective operation

Diverticula of the Intestine

Beginning with the diverticulum of the cervical esophagus previously described, diverticula may be encountered at most levels of the alimentary canal

The true *duodenal diverticulum* emerges along the mesenteric border, but it may subsequently extend posterior to the duodenum and appear to arise from the antimesenteric border These sacs may become quite large and some, at least, may be responsible for the vague and indeterminate symptomatology that has been ascribed to them In general, though, duodenal diverticula are asymptomatic, and because of their thin wall and proximity to the common bile duct they are best left alone When excision is decided upon, the diverticulum may be excised and its neck inverted into the lumen of the duodenum from the outside, or, the inversion may be performed (more satisfactorily, we feel) with the aid of longitudinal duodenotomy that is subsequently closed transversely

Another duodenal defect is the so-called pseudodiverticulum which may occur in association with a chronic duodenal ulcer

Diverticula may involve any part of the jejunum or ileum, but *Meckel's diverticulum* in the distal ileum is the most common of these and is said to persist in from 2 to 4 per cent of infants During early embryonic life it represents the vitello-intestinal duct between the mid-gut and the yolk sac Described by Meckel in 1815, the persistence of this duct in postnatal life may give rise to a variety of pathologic changes. (1) it may contain gastric mucosa which can ulcerate, bleed, or perforate, (2) it may become inflamed and even become gangrenous, usually being found at operation for suspected appendicitis, (3) it may invert as the leading point of an intussusception, (4) it may encircle the bowel and produce obstruction, (5) various segments may remain, attached either to the distal ileum, the umbilicus, or both, and form cysts, (6) finally, it may persist as a fistula from the bowel to

the abdominal wall. Incidentally, the diverticulum may vary in size because of the contraction of muscle in its wall

Treatment consists of placing a clamp transversely across the base of the diverticulum, excising it, and inverting the stump (Fig 274)

Diverticula of the colon are far more common than in other portions of the bowel, and they increase in incidence both with distance from the cecum and with age (incidence 5 per cent above age 40) *Diverticulosis* is the term used for the mere existence of the diverticula, whereas *diverticulitis* denotes actual inflammation of one or more of the defects

The main clinical features of these diverticula are the complications attending inflammation and hemorrhage If the defect has a wide mouth and drainage is free, inflammation and perforation are less likely to occur Bleeding usually occurs because of erosion of the arteries to the diverticulum as they course through its narrow neck.[33] Such hemorrhages may occur in the absence of the usual symptoms and signs of "left sided appendicitis" Chronic inflammation and suppuration may lead to the formation of fistulous communications with contiguous organs including the urinary bladder, small bowel, or another part of the colon.

The *treatment* of the several complications of diverticulosis of the colon will depend upon the condition encountered. The initial attack of diverticulitis is usually treated conservatively, or with proximal colostomy if perforation (or obstruction) has already occurred when the patient is seen. Recurrent attacks usually lead to surgical resection of the involved loop of bowel, particularly as it may be impossible to rule out carcinoma on barium enema alone. A fistulous communication with the bladder wall is excised this is frequently preceded by a diverting colostomy which is later closed Whereas, in the past resection of the involved bowel was rarely performed without the protection of a proximal colostomy, primary resection has been increasingly employed in recent years

That bleeding in a given case of massive gastrointestinal hemorrhage is arising from a diverticulum of the colon may be exceedingly difficult to establish Decision may be rendered particularly difficult when barium enema reveals that the entire colon contains such defects Each case must be decided on its own merits.

Intestinal Neoplasms

Tumors of the small bowel are relatively rare but tumors of the colon are common

Small intestinal neoplasms may be composed of the various cellular elements of the bowel wall, as well as ectopic tissue such as pancreas. Among these tumors are carcinoma, leiomyoma, leiomyosarcoma, lymphoma, fibroma neurofibroma lipoma and simple adenomatous polyp In general, tumors cause obstruction intussusception, or hemorrhage. The carcinoid tumor may also give rise at times to 'serotonin crisis" Multiple polyposis of the alimentary tract may represent a familial manifestation associated with brownish pigmentation of the mucosal surfaces, palms and soles This syndrome was first described by Peutz in 1921[36]

Tumors of the colon include those listed for the small bowel Adenomatous polyps are common, and many believe that carcinoma of the colon is derived from such lesions in most instances *Multiple congenital polyposis* represents an hereditary condition in which the colon may exhibit literally hundreds of polyps Reluctant as the surgeon might ordinarily be to resect all or almost all the colon in the instance of multiple familial polyposis he can assure the patient that the chances of his having developed a malignancy of the colon by the age of 65 are almost 85 per cent. Therefore, either colectomy or ileoproctostomy must be done. We prefer to compromise slightly and perform an anastomosis of the ileum to the large bowel as deep as possible below the

pelvic floor Residual polyps are then fulgurated through the proctoscope at 3-month intervals This has proved satisfactory so far, and the patients are much more satisfied with this than with ileostomy, especially if the early postoperative diarrhea subsides to from 3 to 6 loose stools per day

Characteristically, malignancies of the right half of the colon are associated with anemia and weight loss, perhaps in addition to pain and a palpable mass In contrast, tumors of the left colon far more often cause obstructive phenomena, since by the time the fecal stream has reached this level it is less liquid Nevertheless, the clinical findings in tumors at the extremes of the colon may overlap considerably from case to case

While there can be no doubt that a patient with a satisfactory ileostomy can be largely rehabilitated, it certainly could not be stated that he is a normal person either emotionally or physiologically (which are, of course, mutually interdependent—for the patient is not normal physiologically if he is abnormal emotionally, and *vice versa*)

"Ileostomy: Problem or Solution?"[53]

An ileostomy may be subject not only to the usual complications of the other attempt at an abdominal anus (colostomy) but has certain complications all its own It may prolapse, retract, obstruct, stenose by skin stricture, or be the avenue for hernia formation, as may colostomy In addition, the ileostomy may pour a large volume of liquid into the receiving bag, producing a serious problem in fluid maintenance Perhaps most annoying of all, though, is the frequency with which fistulas and sinuses form just at or beneath the skin, with attendant infection and skin excoriation Of course, skin excoriation may occur apart from fistula formation Regional enteritis has been reported to develop adjacent to the ileostomy in some cases Finally, emotional problems are large in these patients, and such upsets are often reflected promptly in increased difficulty in managing the ileostomy

In reviewing their experiences with ileostomy in 145 patients, Lyons and Garlock found 47 (32 per cent) major complication and during a 15-yr period 20 per cent of a ileostomies required reoperation for compl cations They expressed the prevailing con sensus, namely, that ileostomy (and colec tomy) should not be considered the primar form of therapy for ulcerative colitis, bu that when used to salvage invalids or t save life, the operation permits restoratio of most normal social, sexual, and econom activities

Anatomy and Physiology of the Colon—Further Considerations

A number of facets of colon pathophysiology have already been touched upon The bowel is approximately 5 ft in length and its parts are the cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid, rectum, and anal canal In general, the diameter of the colon is greatest at the cecum and diminishes as it progresses toward the rectum The ascending colon and the transverse colon are supplied by branches of the superior mesenteric artery, whereas the left colon is supplied by the inferior mesenteric artery However, so extensive is the marginal circulation of the left colon, from branches of the middle colic to anastomoses with the middle hemorrhoidals, that the inferior mesenteric artery can be ligated (as it usually is in resections of the lower aorta for aneurysm or occlusive disease) without causing gangrene of the colon

The chief physiologic function of the colon is its rôle in reclaiming water from the liquid ileal stream and its reservoir function at the rectum There is little evidence that other absorptive activities are significant

The colon has both sympathetic and parasympathetic innervation (Fig 259), in addition to its intrinsic ganglia By and large, sympathetic fibers are inhibitory, whereas parasympathetic fibers increase motor and secretory activity. The innervation of the colon is of particular pertinence in ulcerative colitis and congenital megacolon

Appendicitis

ETIOLOGY In contrast to acute cholecystitis or pancreatitis, acute appendicitis is essentially a bacterial infection which may involve all portions of the organ. Unquestionably simple acute appendicitis may occur repeatedly without perforation of this organ. Rupture of the appendix is likely to occur, however, when a fecalith obstructs the mouth of the blind tube and cannot be expelled by appendiceal peristalsis This represents closed loop obstruction and, even if pressure necrosis adjacent to the fecalith does not occur, swelling at the base of the organ may occlude the blood supply to such an extent that with the additional ischemic effect of infection, perforation of the wall occurs[54] One reason that a greatly distended salpinx does not rupture so readily as does the appendix is that the former derives its arterial blood supply from both ends, while the appendix receives its blood supply from only one end

When the appendix ruptures it introduces into the surrounding peritoneal cavity a highly contaminated material, containing streptococci, colon bacilli staphylococci anaerobes and other bacteria. Often the omentum and surrounding organs wall off the material to form a localized abscess, but in some adults and many children this is not accomplished, and spreading peritonitis develops. When this occurs it may prove fatal because of bacterial toxemia, renal failure, hepatic abscesses or intestinal obstruction. Yet a surprisingly large number of patients who are admitted more than 24 hr following perforation are able with supportive therapy (nasogastric suction penicillin streptomycin intravenous fluids and blood plus suitable sedation), to localize the peritonitis with abscess formation They are readmitted in from 6 to 12 weeks for interval appendectomy In one large municipal charity hospital in which I worked, most of the patients admitted with appendicitis had already suffered perforation from one to several days previously these individuals were almost all managed conservatively and the overwhelming majority recovered, to return for appendectomy at a later date

SYSTEMIC REACTION The clinical findings in acute appendicitis are those produced by any acute suppurative process, with certain additional overtones derived from its anatomic location and the fact that it involves bowel The pain, tenderness, and rigidity in the right lower abdomen are associated with tachycardia, fever, leukocytosis, and anorexia with or without nausea and vomiting. The patient who is hungry rarely has acute appendicitis Colicy pain may be due to appendiceal peristalsis when the mouth of the organ is occluded

The differential diagnosis of appendicitis involves at one time or another the exclusion of many other possibilities Moreover, the diagnosis of appendicitis may prove most difficult at the extremes of life The elderly patient may exhibit few signs and symptoms prior to perforation, which he is poorly equipped to survive Abdominal examination in infants is not always easy

The *treatment* of appendicitis consists of appendectomy, if the organ has not perforated or has probably been perforated for 12 hr or less, that is if gross bowel distention is not already present It is in the patients with early perforation that most disagreement will be encountered among different surgeons regarding whether or not to operate. Patients with obvious peritonitis and abdominal distention should be managed conservatively, in our opinion, unless individual circumstances dictate otherwise We retain an open mind concerning operation in children with early peritonitis We once were under the impression that because of a short omentum children had a limited capacity to localize the infection, but our subsequent experience has convinced us that children have a considerable ability to do this

Chronic Idiopathic Ulcerative Colitis (Fig 126)

DEFINITION Ulcerative colitis is a condition in which shallow ulcers are found in various parts of the colon or throughout t

colon, and occasionally even in the distal ileum This process may continue with various remissions and recurrences until it finally reaches a stage that is generally referred to as chronic ulcerative colitis There are, of course, many specific types of ulcerations of the colon, such as amebiasis, carcinoma, bacillary dysentery, and certain granulomatous lesions Nevertheless, so-called idiopathic chronic ulcerative colitis is, as the term implies, a condition for which no definite etiologic factor has ever been established The bacterial theory has now given way to a growing realization that if emotional conflict is not the principal cause, it certainly is a prominent factor in the pathogenesis of this disease It tends to occur in individuals of a particular temperament, it is often improved when their environment can be made less frustrating, and sudden emotional upsets may produce a relapse within 24 hr—undoing the beneficial effects of weeks of hospital care

Following the demonstration that lysozyme, which destroys the protective mucous coating of the bowel, was often much increased in patients with ulcerative colitis, it was considered possible that this was the initiating factor which exposed the mucosa to bacterial invasion More recently, though, it has been the consensus that the increase in lysozyme is more likely an additional effect of the process rather than its cause The disease remains idiopathic

GROSS APPEARANCE OF COLON In a majority of cases the process begins in the sigmoid or rectum as a superficial infection On proctoscopic examination one sees a markedly hyperemic, friable mucosa, with many small hemorrhagic ulcerations which may later coalesce Almost any point that the sigmoidoscope touches bleeds readily, and the examination is likely to be quite painful to the patient Later the infection involves the submucosa and eventually all layers of the bowel, resulting in a scarred, narrowed, and shortened colon which loses its haustral markings, as seen on barium enema

In the later stages, fistulas may form between the colon and the bladder or between loops of bowel, and there may be sinuses around the anus Pseudopolyposis is characteristic of the subacute and chronic phases of the process, and the reported incidence of carcinoma in such polyposis has ranged from approximately 5 to 15 per cent, though the latter figure has seemed excessive to us

SYMPTOMS The symptoms are those of an infectious process and include fever, malaise, weakness, prostration, weight loss, and later anemia Tenesmus and bloody diarrheal stools mixed with mucus and pus are characteristic of the periods of active disease These subside during remissions

PHYSIOLOGIC BASIS OF THERAPY Medical treatment, including mental rest, physical rest, and general hygienic measures should be given a most thorough trial Psychotherapy is helpful in some cases, but few indeed are truly rehabilitated by psychiatric guidance Diet, transfusions, antibiotics, cortisone, and ACTH may be utilized Satisfactory permanent remissions are not uncommon

Surgery, usually consisting of ileostomy and total colectomy, is reserved for fulminating acute cases which threaten to overwhelm the individual and for complications such as intestinal obstruction, perforation, abscess formation, fistula, bleeding, malignancy, or intractability to conservative management

Congenital Megacolon (Hirschsprung's Disease)

This condition appears in two forms The first is that of chronic constipation on a habit or psychologic basis, and this should be treated conservatively The second, or true megacolon, is due to a relative paucity or absence of autonomic ganglia in a portion of the colon through which fecal material is not propelled normally This spastic or narrowed segment of distal colon, involving the rectum and variable lengths of the colon proximally, must be entirely excised to achieve uniformly good colon function postoperatively This is ensured by means of

frozen section control at operation, the line of resection being carried proximally until ganglia are demonstrated microscopically The colon containing ganglia is then brought down and anastomosed by the "pull-through" technic to the rectal pouch distally

The "pull through" for megacolon was advocated by Swenson,[53] and his experience has been extensive and gratifying. In 108 patients so managed through 1953, there had been only one recurrence, this one was due to incomplete resection before frozen section control of the line of resection became routine Moreover, operations in adult male patients have not resulted in impotence In 47 per cent of the patients the defective colon did not extend above the pelvic peritoneum Swenson found that following adequate resection and pull through anastomosis there were 1 to 2 bowel movements a day and that no special diet, laxatives, or enemas were required The abdominal distention gradually disappeared, and the abdominal contour was normal one year after operation Barium enema examinations demonstrated that the dilated bowel returned to essentially normal size and the colon developed the capacity to empty itself completely

One hazard attending attempts at colon cleansing in youngsters with congenital megacolon is that of water intoxication due to the excessive retention of enema water The use of saline enema fluid or the monitoring of plasma electrolyte levels is indicated

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Chapter 15

The Circulatory System

Included in this chapter will be the following topics: the general circulation, body temperature regulation, the heart and great vessels of the thorax, and the peripheral vessels.

The General Circulation (Fig. 127)

Factors in Normal Blood Pressure Maintenance

Basically, the maintenance of a normal blood pressure rests upon the triad of effective heart action (the pump), an adequate circulating blood volume (something to pump), and peripheral resistance (something to pump against). That is, to maintain a pressure above simple hydrostatic levels in a closed system which is physiologically the situation in the vascular bed, an effective pumping mechanism must be combined with fluid to pump and resistance to pump against. A significant defect in any one of these three essential elements will result in arterial hypotension which, in most clinical circumstances, will represent shock. With this general thesis in mind, then let us now consider causes and effects of the failure of separate members of the triad.

THE HEART. An adequate volume of cardiac output is essential for the maintenance of a normal blood pressure. Accordingly, when diminished venous return or heart disease results in a diminished cardiac output, the blood pressure falls and shock is said to exist.

Causes of inadequate cardiac function. The general surgeon is usually concerned with whether or not the heart can support the patient through the anticipated surgery, rather than with heart disease as such. Yet, as will be seen later, the cardiac surgeon and the internist now have a mutual interest in almost every heart lesion, though surgical management in some forms of heart disease is far more successful than in others. Numerous types of heart disease will be considered later, but for the purpose here several general statements will suffice.

Valvular heart disease is detected on physical examination and if the individual is not and has not been in failure, the necessary surgery will usually be withstood satisfactorily. If there is serious doubt regarding compensation, usually digitalis and mercurial diuretics should be employed to prepare the patient for surgery.

Coronary insufficiency may be suggested by a history of anginal attacks, and it can often be diagnosed with an electrocardiogram (ECG). If significant myocardial ischemia is reflected in the tracing, great care should be exercised in recommending elective surgery, for the patients with coronary insufficiency are apt to tolerate surgery less readily than patients with only valvular disease, particularly those with mitral regurgitation. Aortic valvular disease of a severe grade represents an apparent exception, but coronary insufficiency may constitute an important part of the total clinical picture in aortic valvular disease. Mitral stenosis of a severe grade is of course a contraindication to elective surgery until valvulotomy has been performed.

It is a good practice to perform an ECG prior to elective surgery on any patient

NORMAL PRESSURES THROUGHOUT THE CIRCULATION (mm Hg)

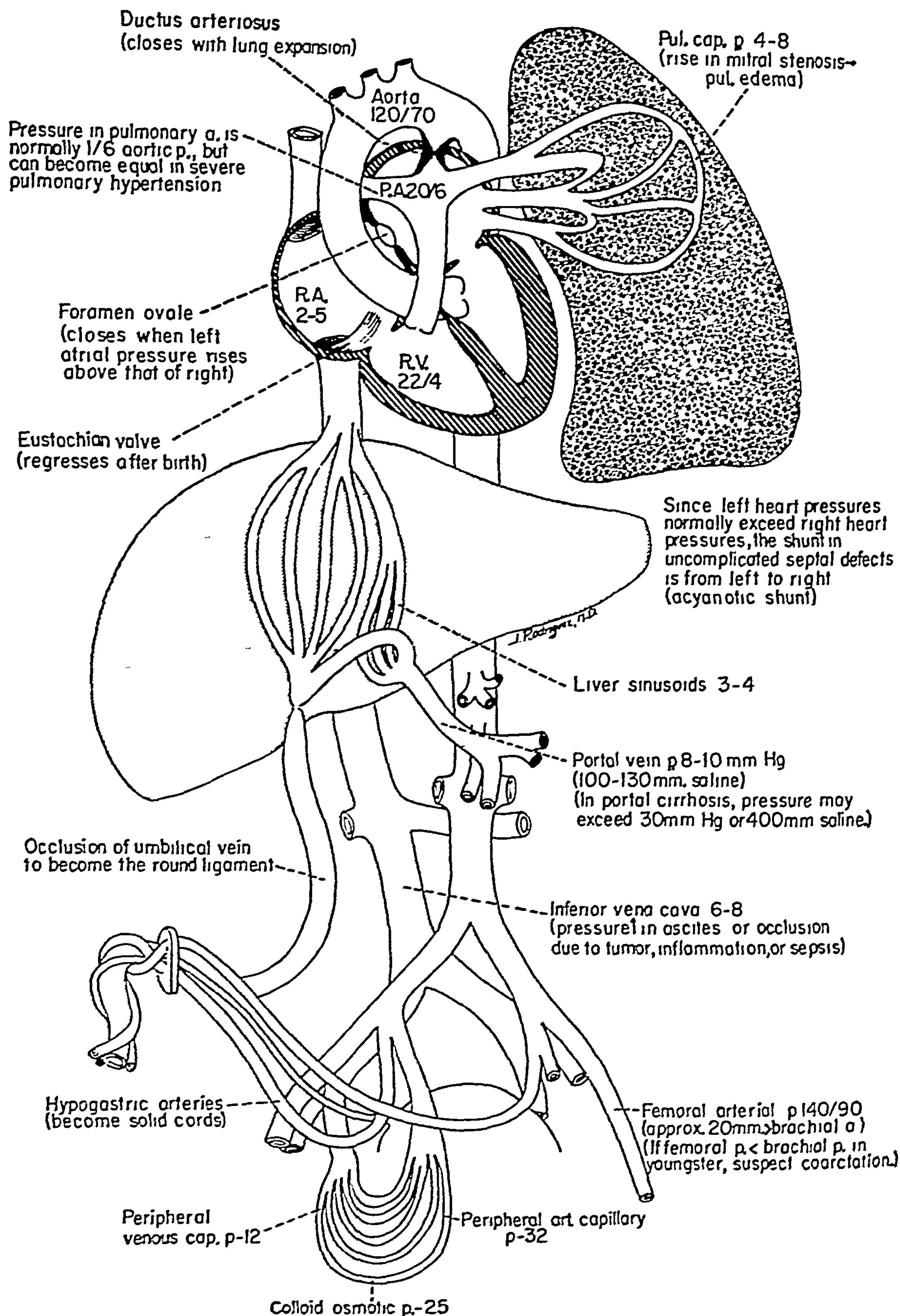


Fig 127 The purpose of this diagram is to make available in one place many of the different normal pressures that the clinician needs to know at one time or another. Opportunity is also taken to indicate what happens to some elements of the fetal circulation at birth. For instance, there is evidence that closure of the patent ductus arteriosus is effected by means of the altered hemodynamics produced by expansion of the lungs.

over 50 years of age Should previous myocardial infarction be revealed, the entire plan of surgical management may need revision. Moreover, the tracing may be invaluable as a "control" later

Blood volume changes have much to do with cardiac function in surgical practice The effects of an inadequate blood volume have been considered in various sections of this volume and will be further analyzed below. Therefore, the deleterious effects of excessive blood volume need only be mentioned here Excessive blood transfusion can so overload the heart as to precipitate clinical evidence of failure and this hazard is particularly great following pneumonectomy In fact, excessive transfusion is only slightly less hazardous than inadequate transfusion, especially in children The following case is illustrative

Case study —A girl 6 years of age fell from a swing and struck her left flank against a wooden stake. Although the skin was not broken, gross hematuria suggested injury to the left kidney, and this was confirmed by demonstrating perinephric extravasation of the radiopaque medium on intravenous pyelogram. Since the hematocrit continued to fall, she was operated upon and the still bleeding fracture of the kidney was sutured She had received 500 cc of blood the day prior to operation and 2000 cc during the procedure. Although blood loss was not measured bleeding was at times brisk. Unfortunately, at the close of operation pulmonary edema was manifested by râles and frothy pink tracheal secretions. Tracheotomy, positive pressure ventilation, venous tourniquets and finally phlebotomy saved the day but death was barely averted. This child weighed perhaps 60 lb or 27 kg. and the normal blood volume was probably less than 90 cc per kg., or approximately 2500 cc She was unquestionably given a marked excess of blood and almost died because of it.

Comment on heart failure due to heart disease —The presence of cardiac insufficiency is reflected in dyspnea and cyanosis abnormal fluid collections in dependent portions of the body, increased central venous pressure, reduced exercise tolerance, and all the other familiar clinical manifestations Yet, there has been much disagreement regarding the mechanisms by which the clinical signs of heart failure are produced Since so many different lesions may produce cardiac insufficiency (*e g*, aortic valvular disease, mitral stenosis, constrictive pericarditis myocardial infarction, etc) it should not be surprising that superficial differences are encountered in the various conditions. Nevertheless, it would seem reasonable to view the signs of heart failure as being derived primarily from failure of the heart itself, regardless of what the secondary effects are Moreover, heart failure represents the end result of a circumstance in which the cardiac output is inadequate for the physiologic requirements, whatever these may be at the time For example, in hyperthyroidism so called "high output" failure may be encountered, where the heart fails even though the cardiac output is far above a normal level, here too, however, the cardiac output is inadequate to meet the metabolic demands A second instance of high output failure is that caused by anemia.

Secondary to the impaired cardiac output, due to disease of the heart itself, is deranged renal function As a result perhaps of both diminished glomerular filtration and increased tubular reabsorption salt and water are retained as edema, pleural effusion, and ascites Altered liver metabolism of adrenocortical and posterior pituitary hormones, as well as variations in the rates of secretion of these substances may also represent factors in the altered fluid metabolism.

Patients in cardiac failure can usually withstand essential surgery, but they should be brought to operation only after meticulous preparation by increasing cardiac reserve with full digitalization (where indicated) and with mobilization of abnormal fluid deposits with diuretics and other measures.

Measurement of cardiac output The fun

tion of the heart is to eject blood, and the cardiac output per minute reflects the work it performs Cardiac output (C O) may be measured by a variety of methods, but only three will be described These are the direct Fick, the blue dye, and the ballistocardiographic methods

The direct Fick method —In 1870 Fick[53] proposed the principle that the rate of blood flow through an organ could be determined by measuring the arteriovenous difference of a metabolite and by measuring the amount of the metabolite consumed over a definite period of time Gréhant and Quinquaud[65] later applied the Fick principle to the measurement of cardiac output in dogs In 1928 Forssmann,[56] in a series of experiments on himself, was able to catheterize the right heart, and in later years Cournand and Richards[39, 74] developed this technic to an extent which rendered the direct Fick method widely applicable in man For the development of this technic Forssmann, Cournand, and Richards were awarded the Nobel prize in 1956

In brief, a cardiac catheter (Fig 128) is passed through an antecubital vein, through the right heart, and into the pulmonary artery Mixed venous blood samples are drawn through the catheter for oxygen analyses, and a peripheral blood sample is taken from a femoral artery, the oxygen consumed per minute is determined by some means such as the use of the usual basal metabolic rate (BMR) machine The cubic centimeters of oxygen consumed per minute, divided by the arteriovenous oxygen difference in volumes per cent, gives the number of 100 cc volumes ejected by the heart per minute, this figure, multiplied by 100, gives cardiac output in cubic centimeters per minute For example, let it be assumed that the arterial oxygen content was 20 vol per cent and venous oxygen content was 14 vol per cent, and that oxygen consumption was 300 cc per minute Then, 300 cc of O_2 per minute/$20 - 14 = 300/6 = 50$ separate 100-cc vol of blood per minute Then, 50×100 cc $= 5000$ cc or 5 L, the cardiac output per minute

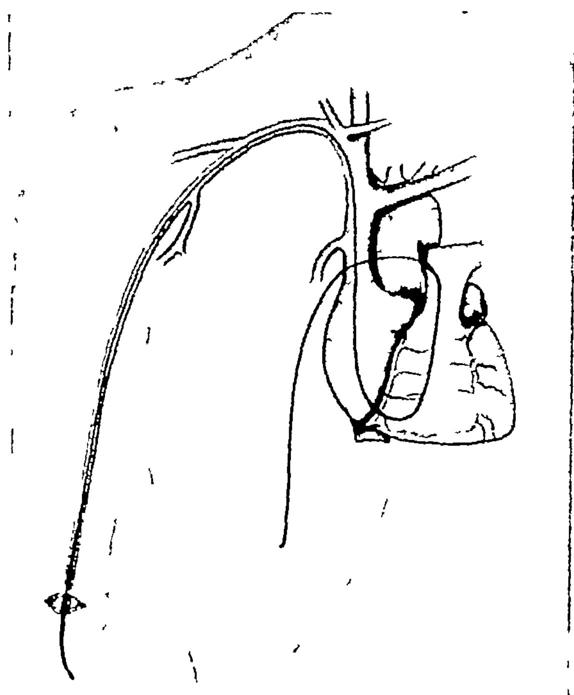


Fig 128 To data obtained by right heart catheterization can now be added those obtained by left heart puncture

The direct Fick method, while very frequently used, suffers from certain disadvantages First, the measurement of cardiac output by this technic requires a venous cut-down in the antecubital fossa This limits the number of separate catheterizations that can be accomplished in any one patient Second, there are occasions when the catheterization is unsuccessful and other occasions when it is decidedly inconvenient, if not clinically inadvisable, to move a seriously ill patient to the fluoroscopic room for the catheterization procedure Therefore, although the direct Fick is often accepted as possibly the most accurate method available, it does have limitations

The blue dye method —In 1897 Stewart[146] perceived that cardiac output could be measured if a substance were infused at a constant rate into a vein so that a concentration plateau could be achieved in the peripheral blood He realized that the measurements had to be made before significant recirculation had taken place In 1928 Hamilton and his associates,[73] while studying circulation times by the single injection method, concluded that the mean concen-

tration of the injected substance in arterial blood was inversely related to cardiac output Later Kinsman and co workers[93] demonstrated that following a single injection of a substance it was possible to correct for the recirculation by plotting the concentrations of timed arterial samples on semilogarithmic paper, and this is essentially the method that is in use today To apply the dye injection principle, one can use either the kymographic method of Hamilton and associates[74] or a more elaborate automatic recording device such as that described by Friedlich, Heimbecker, and Bing.[59] With the kymograph method a measured amount of Evans blue dye is rapidly injected through an antecubital vein, and blood samples are obtained from a femoral artery at timed intervals as the drum upon which the tubes are mounted revolves Cardiac output is computed by constructing a curve from the concentrations of dye in the various tubes, plotted against filling times from the instant of dye injection. From the contour of the curve (Fig. 129) and the amount of dye injected, cardiac output is computed.

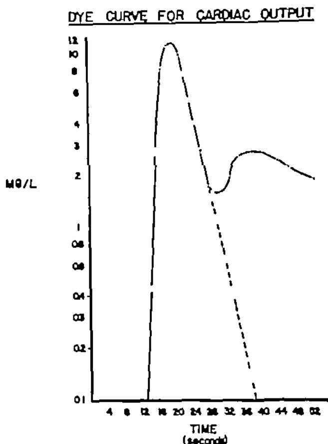


Fig 129 The curve is constructed from multiple timed arterial blood samples following rapid intravenous injection of the blue dye The secondary peak is caused by recirculation. (From Wilson F C Jr., Neely W A., and Hardy J D The blue dye method for the measurement of cardiac output. Surgical Forum 4: 88, 1954)

One advantage of the dye method is that the measurements may be performed on the sick patient without the necessity of moving the subject to the fluoroscopic room, and a second advantage is that multiple measurements of cardiac output can be made. A disadvantage is that it is not always possible to obtain suitable serial samples from the femoral artery

The ballistocardiographic method —As early as 1905 Henderson[80] noted that the ballistic impulses of the human body were somehow related to cardiac output, for he had observed that breath holding reduced the magnitude of the impulses recorded by his machine. In 1939 Starr and associates[143] developed the ballistocardiograph to a point of clinical usefulness and derived a formula relating the magnitude of the impulses to stroke volume With this instrument the downward recoil of the body caused by the ejection of blood from the heart and the upward recoil caused by the blood's striking the aortic arch, are magnified and recorded on paper which resembles that of the ECG The magnitude of the excursion is, with certain qualifications, proportional to the stroke volume. Since the pulse rate is also measured with a suitable timer, the stroke volume can be multiplied by the pulse rate and an approximation for the cardiac output per minute obtained

Comment on methods for measuring cardiac output —We undertook a clinical comparison of the dye, Fick, and ballistocardiographic methods in 22 normal subjects, and found reasonably good correlation between them under normal conditions[117] However, the ballistocardiographic method was frequently not applicable in critically ill subjects, since the ballistocardiographic complexes were so abnormal as to preclude accurate interpretation. The dye method was

most useful in a study of cardiac output in burn patients (Incidentally, cardiac output may be measured by the dilution of an injected isotope as well as by dye dilution). While the dye method has much to recommend it, the direct Fick method will probably continue to enjoy the prestige accorded a reference method until a more generally satisfactory method has been advanced The Fick is particularly applicable in cardiac patients, since the catheterization permits pressure and oxygen analyses in various portions of the right heart, pulmonary arteries, and vena cavae, depending upon the requirements

The ballistocardiograph may prove to have its greatest usefulness in the early detection of individuals with myocardial diseases and impaired functional reserve. Starr[144] found, in a series of normal persons followed for many years, that the ballistocardiograph gave evidence of myocardial hypofunction years before actual coronary occlusion or angina appeared Furthermore, it has been shown that the normal person does not exhibit changes in the ballistocardiograph following smoking, whereas the person with borderline myocardial ischemia often shows marked changes following smoking Cardiac metabolism has been studied under various circumstances by means of coronary sinus catheterization[24]

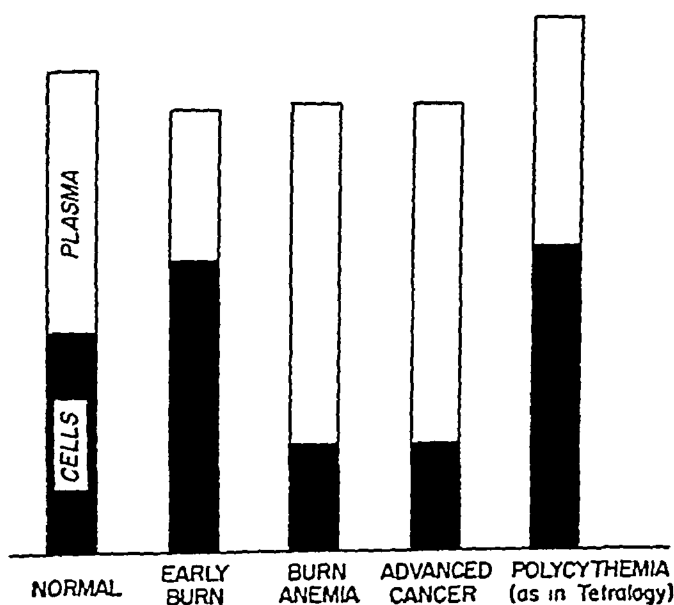


Fig 130 Some variations in hematocrit levels and in total blood volume The proportion of red cell mass to plasma varies in different circumstances, as does total blood volume Moreover, the mass of red cells in 100 cc of blood (the hematocrit) does not indicate the total blood volume—or even the total red cell mass, of course

BLOOD VOLUME The maintenance of an adequate blood volume in the surgical patient is vitally important Indeed, few advances have been more responsible for increased operative safety than has the improved understanding of blood replacement needs during surgery Let us therefore examine some of the factors which influence and regulate the volume of blood under normal circumstances, to be followed by a consideration of the causes of an inadequate blood volume which result in shock

The measurement of blood volume Among the first studies of blood volume were those employing exsanguination Valentin[155] used animals, but Haller[72] used two criminals in 1854 Present methods of blood volume measurement are commonly based upon the dilution of some substance introduced into the blood stream, usually a dye or an isotope The substance should, of course, remain largely confined to the vascular space for a period sufficient to permit measurement Most often the plasma volume (Fig 130) has been determined by the use of Evans blue dye (T-1824), and the total blood volume has been measured using the venous hematocrit The plasma volume may also be measured with radioactive serum albumin (RISA), and the red cell mass may also be directly measured using red cells tagged with radioactive phosphorus, radioactive chromium, or radioactive iron

Since the blue dye method is the one most widely employed clinically (and is as accurate as most), a few words concerning its use are appropriate This dye, for practical purposes, remains within the vascular compartment long enough to permit the measurement of its volume of dilution One may inject 2 cc of the dye intravenously and allow time for mixing Blood samples are

drawn at 10 minutes (and subsequently), heparinized and centrifuged. The concentration of the dye in the plasma is read in a suitable spectrophotometer or Klett-Summerson colorimeter By knowing the concentration of the dye in the circulating plasma after equilibration—and knowing the concentration of the dye (milligrams) in the 2 cc. which were injected—one can compute the volume of plasma in which the dye was diluted (concentration injected × volume injected = measured concentration in plasma × volume of plasma the unknown) This is the familiar $C_1V_1 = C_2V_2$ relationship (Fig. 12) The venous blood hematocrit is then substituted in the following formula to obtain the total blood volume blood volume = plasma volume/1 − hct.

Normal blood volume Blood volume has been correlated with body weight, body height body surface area and with a combination of certain of these The correlation with height or with body surface area is better than the correlation with body weight. The correlation in normal subjects between plasma volume and total body water was examined by Hardy Sen and Drabkin.[78] Subjects were selected to cover a wide range of obesity and it was found that the plasma volume ranged from 2 5 per cent of body weight in the fattest subjects to 5 6 per cent in the leanest subjects with a mean of 4.2 per cent and an average deviation of 22 per cent. However when the plasma volume was expressed as a percentage of the total body water in these subjects who differed so widely in degrees of obesity it ranged from 7.8 per cent in the leanest to 6.2 per cent in the fattest with a mean of 6 9 per cent and an average deviation of 7 per cent. Thus it is apparent that plasma (and blood) volume is correlated more closely with total body water (and with the lean body mass) than with body weight particularly where wide variations in body fat content exist Whereas in the very obese subject the blood volume may amount to no more than 60 cc. of blood per kg of body weight (as fat contains little blood) in the very lean but healthy subject the blood volume may amount to more than 100 cc per kg of body weight Disregarding the extremes of body weight, in the healthy subject of average nutrition (being neither skinny nor fat) the normal blood volume would range from 75 to 85 cc per kg of body weight, this figure can be utilized in the very lean and in the very obese individuals by employing standard optimal weight tables

Physiologic variations in blood volume The blood volume varies somewhat with respect to *age* and *sex* For example, while the blood volume and total hemoglobin do not change significantly after the 20's, the body weight of an average group of men and women increases with age owing to an increase in body fat this results in a reduced blood volume per kilogram of body weight

Nevertheless age variations in blood volume are not due entirely to variations in body fat content. According to Sjöstrand,[141] in women the total hemoglobin diminishes in relation not only to kilograms of body weight but also to height.

Immobilization in bed results in a definite decrease in the total blood volume. The cause of this decrease is not known but the normal volume is quickly regained when the individual resumes normal activity (The calcium balance becomes negative due to increased excretion when a patient is placed at bed rest or is immobilized in a cast this may explain the increased incidence of renal calculi in bedridden subjects)

Intensive physical training produces an increase in both men and women, and the volume of increase appears to be dependent upon the degree of physical conditioning. In a group of especially well trained athletes the increase in relation to body weight was 41 per cent, in another group who exercised regularly but not for competition the increase was only 26 per cent. Since the increase in blood volume and total hemoglobin in these athletes was also demonstrable when

considered in relation to height and calculated basal metabolism, as well as to weight, the increase would not appear to have been due primarily to an increase in muscle mass *per se* [141]

Pregnancy is associated with a physiologic increase in blood volume which appears to follow a fairly linear relationship up to the ninth month, after which it diminishes somewhat; it returns very rapidly to normal after delivery However, the total hemoglobin content does not parallel the increase in blood volume, and the relative hemoglobin concentration consequently declines, resulting in the so-called physiologic anemia of pregnancy

Seasonal variations in blood volume occur, though these are usually not great, the level being somewhat higher in the spring than in the fall. Bazett[11] called attention years ago to the cardiovascular adjustments which attend changes in temperature He noted that hypertensive individuals appeared to be more likely to go into heart failure during the onset of hot weather in the spring or with the sudden appearance of cold weather in the fall He considered it likely that these changes in the clinical condition of these individuals reflected alterations in blood volume and other circulatory adjustments which were necessitated by the changes in environmental temperature The person with incipient heart failure was less able to adjust with required dilatation or constriction of the superficial and deep veins than was the normal individual

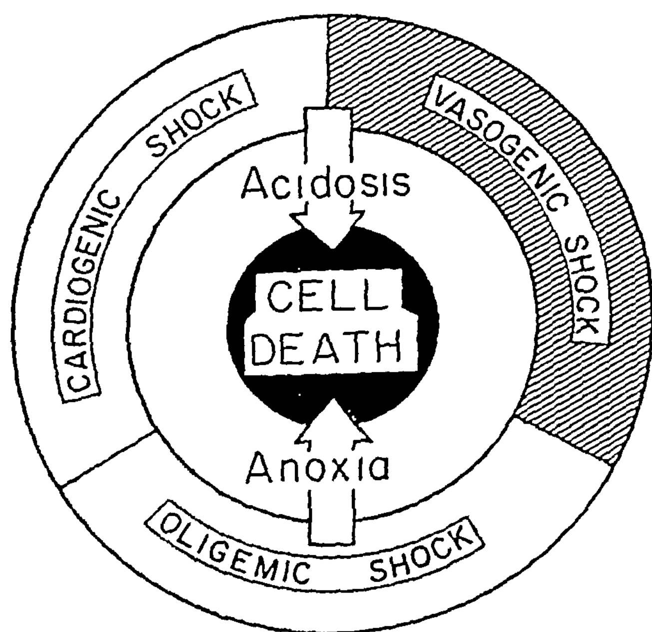


Fig. 131 Anoxia and acidosis are not long tolerated by cells

PERIPHERAL RESISTANCE Having discussed the heart and blood volume, it remains to consider the third member of the triad for blood pressure maintenance, peripheral resistance (Fig 131) Normally the peripheral vessels, particularly the arterioles but to a lesser extent the capillaries and venules, are maintained in various degrees of tonic constriction by the sympathetic nervous system and perhaps other factors If this tonus or constriction of the vessels is excessive and prolonged, actual necrosis of the tissues supplied may occur (see Raynaud's phenomenon, p 421) On the other hand, if the tonus is inadequate, widespread dilatation of the small peripheral vessels may render the vascular bed too large for the amount of blood available to fill it, in this way shock may be precipitated even though the total blood volume is normal Common clinical examples in which hypotension is due to inadequate peripheral resistance (rather than to diminished blood volume or heart disease) are spinal anesthesia, extensive sympathectomy, and autonomic blocking agents Shock due to these causes is readily reversible through the use of vasopressor drugs

The rôle of vascular reflexes in maintaining adequate peripheral resistance upon standing or in other circumstances is quickly apparent when reflex action is faulty. Postural hypotension may be idiopathic, or it may follow illness or extensive sympathectomy, on abruptly assuming the upright position the subject may faint from the fall in blood pressure and resulting cerebral ischemia Ordinary fainting, as from emotional stress or fright, also occurs as a result

both of marked slowing of the heart by vagal impulses and of depression of the vasomotor center

The *carotid sinus syndrome* represents a well known clinical condition which is manifested by fainting when pressure is applied to an abnormally sensitive carotid sinus. Normally the two carotid sinuses have important functions in the regulation of blood pressure (Fig. 132) When their stretch receptors are stimulated by an increased blood pressure or by external means, afferent impulses travel to the vagal center to result in reflex slowing of the heart and to the vasomotor center to produce vasodilatation the blood pressure declines. Conversely lowering of the blood pressure results in afferent reflexes from these sinuses to produce cardiac acceleration and vasoconstriction. A type of sustained hypertension can be produced in rabbits by denervation of the carotid and aortic sinuses. Very occasionally the carotid sinus is hypersensitive and external pressure—as from a stiff collar, particularly on turning the head—may activate the sinus impulses and produce reflex hypotension and fainting. Treatment consists of surgical denervation of the carotid bifurcation the adventitia being stripped for approximately 1 inch both below and above the bifurcation on the involved side or on both sides.

The *aortic* and *carotid bodies* are sensitive to changes in blood pH, O_2, CO_2, certain drugs and to a minor extent, changes in blood pressure. These organs are primarily important in the control of respiration but, like the corresponding sinuses they may have some rôle in *both* respiration and blood pressure regulation (Fig 133)

Shock

CAUSES For practical clinical purposes, arterial hypotension is the most dependable objective criterion of surgical shock (though metabolic changes may not yet have occurred) Furthermore, it has already been seen that a great many etiologic factors may

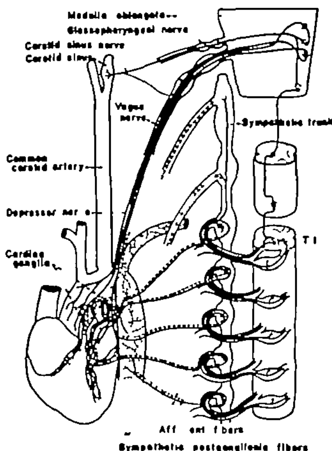


Fig 133 The carotid sinuses and the region of the aortic arch have receptors that are important in regulating blood pressure and heart rate (From KUNTZ, A., *Visceral Innervation and Its Relation to Personality* Springfield Ill Charles C Thomas, 1951)

produce or contribute to arterial hypotension. Again, it is useful to classify the causes of shock according to which of the triad—heart, blood volume, or peripheral resistance—is or are involved (Fig 131) Hemorrhage with reduced blood volume is by far the most common factor in surgical shock, and this is fortunate, for timely blood replacement is gratifyingly effective External bleeding is readily detected, though the volume of loss may not be known, in contrast blood loss into a serous cavity, into the tissues around a fracture or into the bowel may not be promptly detected Aside from actual blood loss, shock may be due to fluid losses from the extracellular space either into 'third spaces" within the body or externally Bacterial endotoxins and anoxia constitute additional hypotensive influences. Various

etiologic factors in shock are given in Tables 14 and 15 (p 361)

Shock which develops during operation is most often due to inadequate effective blood volume Even if no significant volume has been lost, the blood pressure may decline because of vasodilatation produced by the anesthetic, especially if the blood volume was subnormal preoperatively Moreover, in addition to the blood loss (Fig 134) there are other very important sources of hypotension during operation These are an excessive amount of the anesthetic agent, defective pulmonary ventilation, noxious reflexes, inadvertent compression of the inferior vena cava, mismatched blood transfusion, coronary occlusion, and pulmonary embolus, among others

CLINICAL FINDINGS IN SHOCK The cardinal finding in shock is arterial hypotension, and this is usually accompanied by additional signs and symptoms The individual exhibits pallor, cyanosis, sweating, coldness of the extremities, thirst, restlessness, apprehension and, usually, a rapid pulse Such findings should always prompt a blood pressure measurement

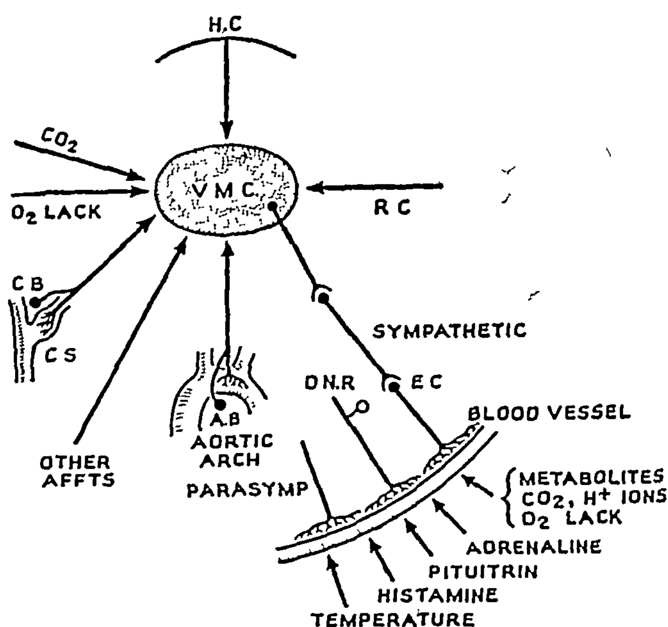


Fig 133 Factors which regulate arterial tone H C = higher centers (cerebral cortex and hypothalamus) R C = irradiation from respiratory center V M C = vasomotor center C B and C S = carotid body and carotid sinus D N R = dorsal nerve root fibers (From WRIGHT, S *Applied Physiology*, Ed 9 London, Oxford University Press, 1955)

The level of blood pressure required for effective renal function varies under different circumstances The chronically starved individual may "normally" exhibit a blood pressure ranging from 80 to 90 mm Hg systolic, a value which ordinarily would represent mild shock Also, a level of 100 mm Hg systolic in a previously hypertensive subject may be inadequate for effective renal filtration

METABOLIC CHANGES IN SHOCK If arterial hypotension is allowed to persist long enough, it will become irreversible By definition, *irreversible shock* is that condition which exists when by no amount of transfusion or other therapy can the blood pressure be restored to a normal level and the patient dies As knowledge unfolds, it is increasingly apparent that many instances of what might appear to be irreversible shock will, in fact, respond to massive blood transfusion or, occasionally, the administration of vasopressor agents such as norepinephrine Yet, if no treatment is effective, irreversible or fatal shock ensues What are some of the metabolic changes that occur to render the shock irreversible?

The metabolic changes that occur during shock were examined by Engel,[52] and it would appear that the various metabolic aberrations are ultimately the result of anoxia The progressive anoxia due to circulatory failure must of necessity lead to cellular and enzymatic disorganization and death Nevertheless, the earliest metabolic responses of shock-inducing stimuli noted by Engel were those common to the response to injury in general, and in these early findings anoxia *per se* played only a small specific rôle As circulatory failure progressed, however, another set of metabolic phenomena began to appear

An early change in *nitrogen metabolism* was the rise in the blood amino acid nitrogen concentration for, as anoxia and shock progressed, a steady and often sharp increase in plasma amino acid nitrogen occurred

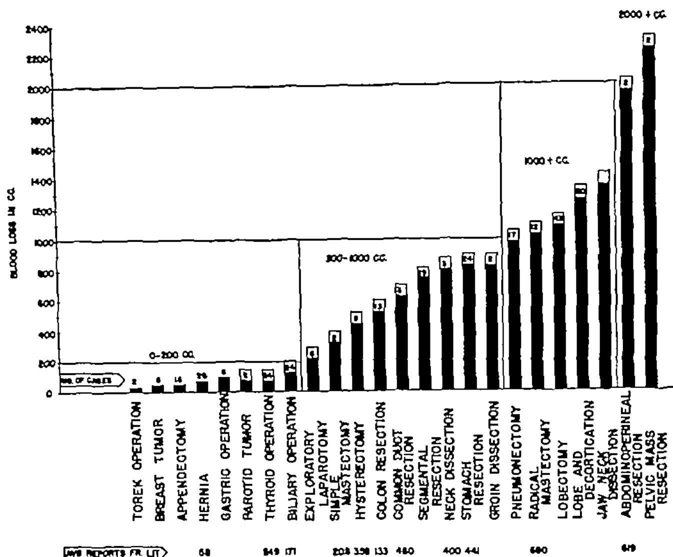


Fig 134 Blood losses at common operations. The loss at any given operation may be much greater than the average and losses at heart-aorta operations are not even included The total volume of blood loss is dependent upon rate of loss and length of operation. (Redrawn from Saltzstein H. C and Linkner, L M J A M A., 149: 722 1952 and from Cole, F H and Lougheed J C J Thoracic Surgery 27: 402, 1954.)

Since the catabolism of amino acids occurs predominately in the liver the rise in amino acid nitrogen concentration in shock drew early attention to the possible rôle of the liver in hypotension A high blood amino acid nitrogen level and a low portal vein oxygen content were associated with an increased mortality in hemorrhagic shock. This was consistent with the earlier demonstration of the dependence of the liver on the portal vein for a part of its oxygen supply and of the failure of this supply during shock. Early in shock the liver is capable of meeting the increased demands for deamination and urea formation but later this activity declines and the blood amino acid nitrogen and ammonia levels rise

The effects of shock on *carbohydrate metabolism* are essentially what one might predict from current knowledge of the anaerobic metabolism of these compounds[32] The blood sugar rises at first during shock and may remain elevated for a considerable period of time As the glycogen content of the liver becomes depleted however and glucose utilization at the periphery increases without compensatory gluconeogenesis or glycogenolysis the blood sugar begins to fall Late in shock there may be considerable hypoglycemia. Blood lactate levels rise late in shock, while muscle glycogen levels decline

Information regarding *fat metabolism* in shock is meager

Unfortunately, these few lines concerning metabolism have been entirely descriptive, not interpretive, for the ultimate chemical changes which transpire to produce irreversible shock remain obscure

RÔLE OF THE LIVER IN IRREVERSIBLE SHOCK. As noted, all evidence indicates that the liver has an important rôle in the genesis of irreversible shock This is not surprising, in view of its central position in normal metabolism, and certain aberrations in nitrogen and carbohydrate metabolism have been given

Among the more thought provoking contributions to the literature on irreversible shock were those of Shorr, Zweifach, and Furchgott [137] These workers postulated and presented supporting evidence for two opposing humoral factors which affected blood pressure One was the vaso-excitor material (VEM), derived principally from the kidneys and similar to or identical with the renin-angiotonin system The opposing physiologic principle was vasodepressor material (VDM), produced by the liver, which opposed the hypertensive or pressor effects of VEM They believed that VDM of hepatic origin fulfilled, in respect to its action on the terminal vascular bed, the requirements of an antagonist to the renal vaso-excitor principle Shorr and his associates felt that the competition between these two principles for control of the terminal vascular bed was seen during the progression of the shock syndrome, particularly in the transition from the hyper- to the hyporeactive phase During this transitional phase both principles were thought to be present in the blood stream, but their concentrations were such as to balance one another, thus permitting the vascular bed briefly to resume a normal type of reactivity It was the hypothesis of these workers that a critical feature of the progressive deterioration of the peripheral circulation during the shock syndrome is a profound impairment in the functional integrity of the vascular bed, especially in the splanchnic area In substance, then, it was proposed that VEM and VDM (considered to be ferritin) are components of an homeostatic mechanism which, under certain conditions, participates in the regulation of peripheral blood flow During the initial phase of the shock syndrome VEM is elaborated by the anoxic kidney and appears in the blood stream In addition to this renal factor, the adrenal medulla and the sympathetic nervous system also contribute to the compensatory response of the peripheral vascular bed The compensatory phase is thus a composite of the activity of renal, adrenal, and neurogenic homeostatic mechanisms, superimposed upon the intrinsic tone of the blood vessels themselves In the latter stages of shock, the terminal vascular bed continues to manifest decompensatory vascular changes and the blood stream exhibits a progressively increased titer of VDM It was considered that this was referable to damage to the hepatic inactivation mechanism which, under normal aerobic circumstances, rapidly transformed sulfhydryl ferritin to its inactive bisulfide form (The liver of shocked animals during the decompensatory phase of the syndrome showed a considerable impairment of the capacity to inactivate ferritin) As VDM accumulates, the eventual collapse of the systemic circulation is said to be associated with an accumulation of blood within the liver and the splanchnic area Finally, the progressive deterioration of the circulation, after a state of shock has been established, would appear to be related to the profound reduction of blood flow in the terminal vascular bed of different tissues

These conclusions regarding VEM and VDM appeared to be further supported by collateral data published by Seligman and his associates [135] They showed that if the liver of the shocked animal could be independently perfused with oxygenated blood, then shock which was usually irreversible could be reversed and the animal saved Later studies by Fine and his associates[54] emphasized the importance of bacteria in producing irreversible shock Using antibiotics, they found evidence which indi-

cated that the removal of the local infection within the gut prevented the development of irreversibility following a standardized shock procedure

It should be pointed out that the VEM-VDM theory of irreversible shock has many aspects that are difficult to prove

Actually, despite the fact that the adrenal cortex and various other organs have been indicted at one time or another, the reason for the irreversibility of terminal shock remains unknown. There is renewed interest in the possibility that heart failure *per se*, rather than peripheral collapse, may be a primary factor in irreversible shock. The rôle of the heart in the genesis of irreversible shock was reviewed by Wiggers[160] in 1947 He himself had demonstrated that myocardial depression does occur in shock and is probably intensified during spontaneous circulatory failure but he concluded that myocardial depression was not the dominant factor responsible for the progressive reduction in cardiac output, the decline of arterial pressure and the deterioration of pulse pressure patterns. After simple hemorrhage a progressive reduction in venous return appeared to be the paramount factor However the coexistence of myocardial depression was considered certainly to be an unfavorable circumstance for it reduced the capacity of the ventricles to expel their diminished blood volume as effectively as after simple bleeding. Consequently, myocardial depression plays an important rôle in the rapid downward trend of blood pressure and is possibly the ultimate cause of death.

This increased awareness of heart failure *per se* may reflect a healthy reorientation in the approach to the shock problem.

THERAPEUTIC CONSIDERATIONS IN SHOCK

THE PREVENTION OF TISSUE ANOXIA. The management of hypotension consists of anticipating and avoiding or of actively treating, physiologic threats to circulatory stability The patient should be brought to operation in the best possible general health Since such conditions as liver disease pulmonary disease heart disease severe malnutrition or acute or chronic infection may contribute to circumstances which predispose to shock, these and other defects should be corrected preoperatively insofar as possible. In addition to these factors that afford a physiologic setting in which shock may readily develop, there are more direct and immediate requirements which must be met in the prophylaxis and therapy of shock in the patient who does not have significant disease of important supportive organs Some of these requirements were listed above, but they will be amplified here in certain respects

Preoperative shock In most patients coming to operation the important causes of shock are deficiencies of water and salt and of blood. The correction of dehydration was outlined in Chapter 2 Chronic blood loss or chronic malnutrition may have produced a serious blood volume deficit particularly in the essential oxygen carrying red cells (Fig. 130) even though various forms of compensation have maintained a normal blood pressure This deficit in red cells may be corrected satisfactorily preoperatively, from a practical point of view, by transfusing the patient over a period of several days until the hematocrit level has risen almost to a normal value Of course the hematocrit level may not reflect the total blood volume deficit in acute hemorrhage for here the hematocrit level may be normal even though the total blood volume may be markedly reduced in chronic blood loss, however, the reduction in the red cell mass (which is often more marked than the reduction in plasma volume or in total blood volume) is usually reflected in a diminished hematocrit level The hemoglobin determination is also of value in the management of these subjects.

The transfusion of say, 2 L of blood in the chronically anemic patient (whose total blood volume may not be greatly reduced) does not necessarily result in a 2 L. increase in total blood volume the red cell mass is augmented by the volume of red cells introduced but the plasma infused tends to leave the circulation. The result is then, that the

transfusion of 2 L of blood may augment the total blood volume by little more than 1 L This is a fortunate circumstance, for thus the red cell mass can be increased without overloading the circulation

When the patient is in shock from acute blood loss—whether external, into soft tissues, or into a serous cavity—he has usually lost more than 1 L If the blood pressure is essentially normal in the supine position but falls precipitously when the individual is made to stand, the blood loss is probably more than 1 L but less than 2 L If the blood pressure in an individual of average size remains at very low levels or is unobtainable in the supine position, a blood volume deficit of at least 2 L exists Furthermore, while the blood pressure may rise to an essentially normal level with the replacement of only 1 L of the deficit, this represents marginal compensation and any blood loss at surgery will be poorly tolerated

The use of blood volume measurements to estimate the volume of blood that may have been lost in an acute hemorrhage is not very helpful, there is rarely available a control measurement performed prior to the hemorrhage, and the normal blood volume varies considerably in different patients In our experience, it is in the patient who may have lost blood into the peritoneal cavity following surgery—or whose blood loss was not closely followed and replaced at surgery—that a blood volume measurement may be most useful If the low blood pressure has not responded to what would appear to represent more than adequate blood transfusion, a blood volume determination may be of considerable assistance in eliminating a serious blood volume deficit as the chief etiologic factor in the shock state

By and large, however, the volume of blood that needs to be replaced in shock due to simple blood loss is that volume which raises the blood pressure Moreover, a prompt rise in blood pressure following blood transfusion is a favorable prognostic sign Hematocrit values do not decline for hours following an acute hemorrhag are particularly of value only in the ma ment of continuing hemorrhage, such curs in bleeding peptic ulcer

Finally, shock in patients coming eration for the management of traum be due to any of the injuries shown ure 1 Again, the fundamental def shock is tissue anoxia, and airway ob tion, head injury, or tension pneumot may each cause shock in the absence o nificant blood loss

Shock during operation Modern su is possible because of an increased awa of the amounts of blood that may b at operation, and the replacement of th as it occurs In Figure 134 are shown age losses at various types of opera but obviously these values do not repr the maximum loss that may occur i given case where excessive hemorrha encountered Therefore, in long abdo procedures where blood loss is not but is continuous, and in thoracic proce where massive sudden loss may occur, highly desirable to maintain an estima the continuing blood loss If sponges ar to be used dry and then weighed afte with blood, the use of suction in lie sponges, where possible, permits contin observation of the volume of blood colle in a graduated suction bottle If bloo being lost and the anesthesia appears s factory, hypotension usually indicate need for additional blood transfusion tients who sustain massive blood loss at eration may have their total blood vol replaced several times over (in one of patients, 28 pints) without ill effect, so l as shock is avoided

While blood volume deficits lead the important additional causes of shock ex the principal ones having to do with anesthesia. Spinal anesthesia diminishes capacity of the patient to make compen tory reflex vascular adjustments to chan in blood volume, furthermore, the los vascular tone and consequent vasodila tion in the lower portion of the body a

splanchnic area may so enlarge the vascular bed that the normal blood volume is now inadequate to fill the available space and a fall in blood pressure occurs. Of course, defective spinal anesthesia may extend so high as to arrest respiration

General anesthesia has its own hazards Vasodilatation is not so likely to result in a precipitous fall in blood pressure, though there may be a more gradual decline. The special hazards of general anesthesia are inadequate pulmonary ventilation with the proper gas mixtures, and excessive amounts of the anesthetic agent. Anoxia may result from an inadequate volume of gas exchange, or from defective pulmonary function *per se*, or, occasionally from a low oxygen concentration in the gas mixture delivered to the patient. Hypercapnia (excessive CO_2) may be caused by insufficient ventilation to remove the carbon dioxide of metabolism, or by defective pulmonary function, or by inefficient removal of the CO_2 by the soda lime canister in the closed system. Different brands of soda lime preparations vary markedly in the efficiency with which they remove CO_2 from the gas flowing through, and the capacity of even the best material is rapidly depleted and must be replaced.

In addition to blood volume deficits and defective anesthesia, the leading causes of shock during surgery a great many other factors may result in hypotension in the occasional case. A number of these have been listed in Table 14. To recognize the cause of the hypotension is usually to institute the proper corrective measures. Cardiac arrest must always be anticipated.[88, 89]

TABLE 14 Causes of Shock during Operation

1 *Blood loss* or antecedent blood deficit
2 Defective anesthesia—cardiac arrest
  a Too much of the anesthetic agent
  b Inadequate ventilation with hypercapnia
  c Inadequate oxygenation
3 Transfusion reaction or excessive transfusion
4 Heart failure from heart disease
5 Others pulmonary embolus coronary occlusion hemiplegia reflexes interference with venous return pheochromocytoma adrenocortical failure and other metabolic decompensation

TABLE 15 Causes of Shock in The Postoperative Period

1 Postanesthetic shock (various factors)
2 Further hemorrhage or unreplaced deficit
3 Pulmonary atelectasis
4 Pulmonary embolus
5 Coronary occlusion
6 Infection
7 Adrenal failure
8 Liver failure
9 Morphine in elderly patients
10 Translocation of fluids

Shock during the early postoperative period Here again postoperative shock is frequently due to inadequate blood replacement during operation, perhaps aggravated by minor but continuing blood loss from the wound or into a body cavity (Table 15) Too complications of anesthesia may extend into the postoperative period. However assuming that blood volume deficits have been corrected and that the anesthesia has been satisfactory there are other important considerations which occasionally arise, though most of these may also occur in a patient who has not been operated upon. Among these are excessive opiate dosage in the elderly subject, cerebrovascular accidents massive atelectasis, pulmonary embolism, myocardial infarction, adrenocortical failure, septicemia, hepatic decompensation, and mesenteric occlusion with gangrenous bowel, to mention a few Moreover, some patients develop refractory shock where no adequate explanation is forthcoming, even at autopsy ("metabolic decompensation)

Adrenocortical failure deserves special comment This condition is rare in nonadrenalectomized patients. When it does occur it is likely to follow prior adrenocortical therapy for some condition such as arthritis resulting in atrophy of the patient s own adrenals or, failure may develop due to involvement of the adrenals with metastatic tumor or rarely, tuberculosis Acute adrenocortical failure that occurs within 24 hours of operation does not permit time for change

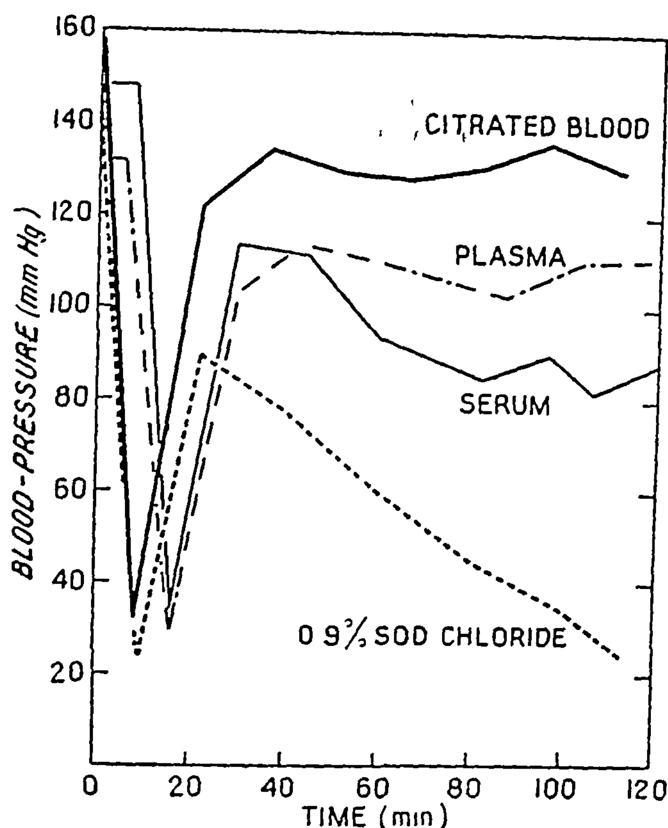


Fig 135 Blood is the best solution to use in replacing blood loss Plasma and serum are helpful Saline is momentarily beneficial, but the effect of the noncolloid (crystalloid) solution is soon dissipated (From BUTTLE, G A H, KEKWICK, A, AND SCHWEITZER, A. Blood substitutes in treatment of acute hemorrhage Lancet, **239:** 509, 1940)

in blood chemistry values to occur Characteristically, a fall in blood pressure is accompanied by a marked elevation in body temperature, a rapid pulse, and disorientation leading to coma *Thus, in acute postoperative adrenocortical failure it is the clinical picture, not laboratory tests, that must prompt and guide replacement therapy* Intravenous hydrocortisone is the treatment of choice, given at a rate of 100 mg per 6 hours

As further causes of metabolic crisis, undiagnosed thyrotoxicosis and pheochromocytoma may be mentioned

Rôle of plasma expanders in the management of shock When blood is not available, even a saline infusion (crystalloid solution) is of some benefit (Fig 135) Far more efficacious, however, is the use of a colloid solution as represented by the various plasma expanders The most commonly used of these are bovine gelatin, polyvinylpyrrolidone (PVP), and dextran Of these, we prefer dextran, which is largely excreted in the urine or metabolized PVP is stored by the phagocytic cells of the body, and gelatin, while quite satisfactory in most respects, is likely to be too viscous for rapid infusion unless it is first warmed We rarely use more than 2 or at most 3 L of one of the plasma expanders, but they serve admirably until blood can be made available There is no substitute for whole blood or, more specifically, for the red blood cells which must transport the oxygen

Rôle of norepinephrine in the management of shock While our opinion regarding the ultimate place of norepinephrine and other pressor agents has not yet crystallized, there is no question but that some patients in shock are saved by these materials We have in mind the individual who has lost no appreciable amount of blood, and in whom generous blood transfusion has had little or no effect Perhaps hydrocortisone has also been tried Here, occasionally, an intravenous drip of norepinephrine will maintain a blood pressure level compatible with life until some obscure type of "metabolic compensation" takes place over a matter of many hours, following which the drug can be slowly withdrawn (Fig 136) Therefore, when blood transfusion and other obviously necessary measures have failed to elevate the blood pressure in apparently irreversible shock, the use of norepinephrine may achieve survival of the patient It is administered at a rate that will maintain the systolic blood pressure level above 90 mm Hg

One hazard of the use of norepinephrine, especially when infused in high concentrations, is that necrosis and slough of the tissues surrounding the site of intravenous infusion may occur, even when no extravasation is detectable Despite the increased probability of tissue necrosis when the higher concentrations of the drug are employed, this risk may be unavoidable when the drip must be maintained for prolonged

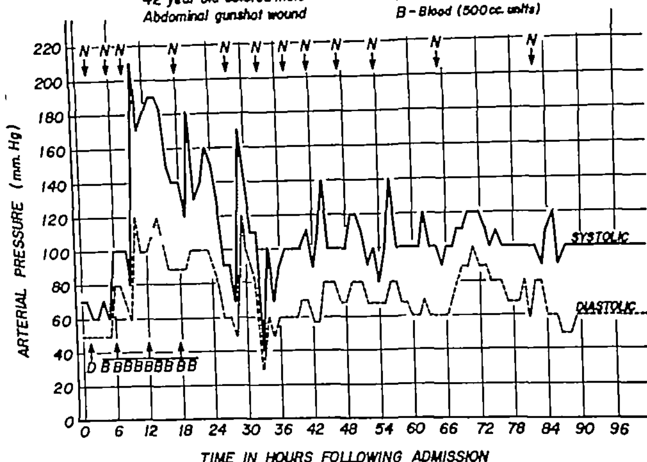


Fig 196 Only with norepinephrine in substantial dosage was it possible to maintain the blood pressure above shock levels until "metabolic compensation" had been achieved at 84 hours following admission. Laparotomy was performed during the first 6 hours. It is very likely that norepinephrine saved this patient's life It has a definite place in the management of nonoligemic shock.

periods, otherwise an excessive volume of fluid might be infused in a patient whose kidneys are not able to excrete the water load.

Controlled Hypotension during Anesthesia

During recent years controlled hypotension has been widely used in the management of hemorrhage in certain types of operation, especially in neurosurgery. The particular objective has been to reduce the rate of hemorrhage that can be so profuse as to threaten the life of the patient despite all therapy, as may occur in the resection of highly vascular tumors or in the management of an intracranial aneurysm. Induced hypotension has also been used to reduce persistent hemorrhage due to a diffuse ooze over a relatively large surface. Most surgeons do not believe that hypotensive anesthesia is justified in essentially routine procedures where bleeding can be controlled by conventional means.

TECHNICS. Controlled hypotension has been produced in three ways (1) arteriotomy, (2) total spinal block, and (3) ganglionic blockade

Arteriotomy or arterial bloodletting at operation was advocated by Gardner and Hale [80] Essentially, from 500 to 3000 cc. of blood was removed from an artery, as required to induce the desired level of hypotension during neurosurgery This was noth-

ing other than ordinary hemorrhagic shock, with all its inherent metabolic risks, and this means of inducing hypotension was not widely embraced

Total spinal block was employed by Griffiths and Gillies[66] in 1948 They reduced the blood pressure to 70 mm Hg or below by the use of spinal anesthesia to achieve paralysis of the entire efferent sympathetic outflow, with lesser degrees of sensory and motor blockade, so that the muscles of respiration and the medullary centers remained relatively unaffected It was believed that the arteriolar dilatation so produced guaranteed normal oxygenation of the tissue cells, and that the decreased cardiac output inherent in the technic was compensated for by the decreased peripheral resistance and, therefore, by the decreased work of the heart[107] Proper posturing and positioning of the patient were considered important also Venous ooze was reduced when the operating field was above the level of the right heart and increased when it was below the right heart

Ganglionic blockade was established as a reasonably safe and effective method of inducing hypotension when in 1948 the safely injectable methonium compounds became available The most frequently used of these have been hexamethonium and pentamethonium, which can readily produce blood pressure levels of from 50 to 60 mm Hg Subsequently Arfonad, a thiolium compound, has also enjoyed extensive use

PHYSIOLOGIC EFFECTS OF INDUCED HYPOTENSION There is now the general impression that physiologic processes are far more normal when hypotension is induced by autonomic blockade, the blood volume remaining normal, than when the hypotension represents oligemic shock, as produced by arteriotomy

Little[107] reviewed the subject of controlled hypotension, including physiologic effects, complications (fatal and nonfatal), indications, and contraindications While definite proof of anticipated brain damage was not obtained by questionnaires and other means, liver and kidney damage certainly did occur in some patients Moreover, he found that the over-all "complication rate following the use of 'controlled hypotension' is amazingly high" In Great Britain and Ireland the rate was 1 in every 32 cases, and in the United States 1 in every 27 cases The most common complication was *reactionary hemorrhage*—excessive oozing after operation The second most common complication was that of a *delayed awakening time* after operation and anesthesia had been terminated *Blurred vision* was third in incidence and *anuria* or *oliguria* was fourth *Arterial thromboses* were fifth, having affected such essential vessels as those to the brain, heart, retina, and bowel *Cardiac arrest* and *cardiovascular collapse* were encountered more often than under ordinary anesthesia

The fatal complications included most of those given above Renal failure, cerebral thrombosis or anoxia, reactionary hemorrhage, and other cardiovascular problems contributed the greatest number of deaths

SUMMARY "Controlled hypotension" represents a highly specialized technic for lowering the blood pressure to avoid what might prove to be uncontrollable hemorrhage By no criterion is the hypotension "physiologic," and it should be induced only when the hazard of exsanguination or of impossible operating conditions without it outweigh the hazards of the induced hypotension An advantage of Arfonad is that its effect is very transient, administered by intravenous drip, moment-to-moment control is possible and when the drug is stopped the blood pressure rises to its previous level With some of the other drugs, vasopressor agents may be required to restore the normal blood pressure

Arterial Hypertension

While surgical management is called for in the correction of hypertension due to coarctation of the aorta, adrenocortical tumors or hyperplasia causing Cushing's syndrome, pheochromocytoma, thyrotoxicosis, or occasional unilateral renal damage, the use of

surgery in the control of essential hypertension is diminishing. Moreover the overwhelming majority of cases of hypertension fall into the "essential" category. Although the cause of essential hypertension is unknown, the consensus is that psychosomatic stress acts in some way upon renal and peripheral arterioles to increase peripheral resistance through the effect of the humoral substance renin that is apparently elaborated by the ischemic kidney. In other words, essential hypertension appears to result from alterations in the neural and humoral control of arteriolar tonus.

Surgical sympathectomy has been replaced by medical therapy employing drugs which lower the blood pressure by acting at various neural levels between the cerebral cortex and the end organs in the arteriolar wall. Commonly used examples of such drugs are Bistrium (hexamethonium) and Apresoline (hydralazine), and the alkaloids of veratrum and rauwolfia. Subtotal and total adrenalectomy have likewise been given an adequate trial as a means of controlling severe essential hypertension, and have not afforded success commensurate with the seriousness of the procedure. Furthermore the necessity for maintaining the lowest tolerated level of adrenocortical function to produce a normal blood pressure—or one that is at least lower than that present preoperatively—results in the constant risk of adrenocortical insufficiency.

Body Temperature Regulation: Normal Physiology, Fever, and Hypothermia

Hyperpyrexia and its causes have always been of concern to the surgeon but the widespread use of hypothermia for extending the safe period of ischemia particularly during open heart surgery has greatly stimulated interest in the mechanisms which influence body temperature under normal and abnormal conditions.

Normal Physiology[47, 136]

AN ANALOGY. The mechanism for the maintenance of a normal body temperature has been compared to the central heating equipment used in many homes. There is a *thermostat*, a *conduction system* of pipes, and a *furnace* to produce heat. For cooling in the summer the same equipment may be used, with the exception that, instead of a furnace a cooling mechanism is turned on.

The body thermostat. Ranson and his associates[35, 123, 126] demonstrated that the hypothalamus contains a body heat-regulating center: heat production was increased (usually by shivering), and heat loss was diminished when the animal was exposed to cold; in contrast, heat production was reduced and heat loss increased when the animal was exposed to heat.

Aside from the fact that there appears to be a fairly definite center for increasing heat production when needed and another for increasing heat loss by vasodilatation and sweating when this is required, with considerable overlapping between the two, one need not enter into the conflicting evidence concerning the precise location of these centers within the hypothalamus.

The furnace. The heating unit of the body consists of the metabolic processes of the cells particularly those of the muscles whose combustion of carbohydrate, fat and protein liberates heat. When additional heat is required the tone of the muscles is increased and, presently, if the exposure to cold is prolonged, visible shivering occurs which increases muscle activity and sharply increases heat production.

The conduction system. The conduit system of the body temperature regulating mechanism consists of the blood vessels, the blood volume and, to a lesser extent, body water other than that contained in plasma. Heat from the interior of the body is carried to the surface by the blood for elimination and, conversely, cooling of the blood flowing through the surface vessels lowers the central temperature of the body.

INTEGRATION OF THE THERMOREGULATORY CENTER, HEAT PRODUCTION AND HEAT DISSIPATION. In essence body temperature represents the net balance of body hea

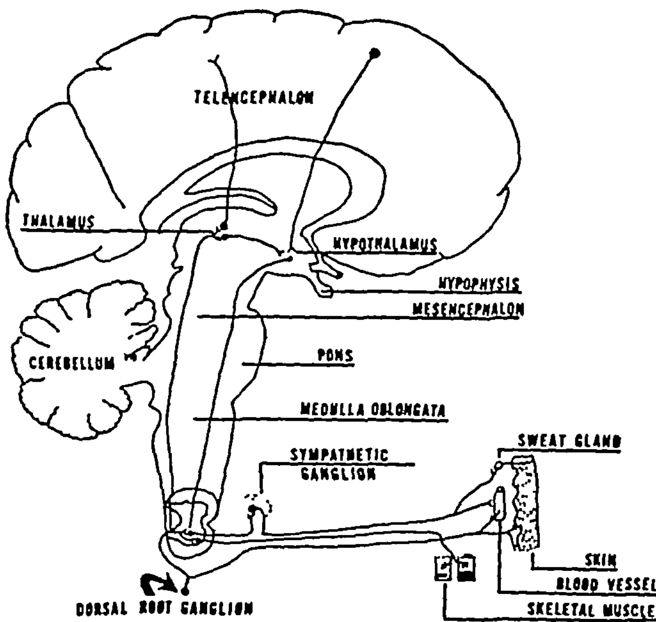


Fig 137 Sketches prepared by Dr Joseph C Hinsey showing the relationship of the nervous system to the control of temperature (From DuBois, E F *Fever and the Regulation of Body Temperature* Springfield, Ill, Charles C Thomas, 1948)

production or absorption, as against heat loss An increased body heat production or absorption, without a proportionately increased heat loss, will result in a rise in body temperature (fever) Similarly, an increase in heat loss which is not balanced by an increase in heat production will result in a fall in body temperature (hypothermia) The neural mechanisms which control body heat regulation are shown in Figure 137 Represented are the hypothalamic connections, the musculature for the production of the largest portion of endogenous heat, and the skin, blood vessels, and sweat glands, which are responsible for the distribution of heat and for the elimination or absorption of heat When environmental temperatures reach 95° F, heat dissipation is achieved largely by sweating, with the cooling effect of vaporization of this sweat

Experimentally, when a dog with an intact heat regulating center is exposed to a lowered environmental temperature, shivering begins and continues throughout the duration of the exposure to the lowered environmental temperature When an intact dog is exposed to an increased environmental temperature, panting continues throughout most of the time that the
is exposed to this increased enviro
temperature However, when the h
ulating centers are destroyed, the
longer responds to cold by shiveri
rectal temperature may fall from 3
perhaps 28° C, rising again when the
is returned to room temperature
verse may also be demonstrated,
that when the intact dog is expose
increased environmental temperatu
is only a moderate rise in body temp
whereas in the dog whose heat reg
centers have been destroyed there i
fort to compensate for the increas
absorption from the surrounding air,
rectal temperature rises markedly [91]

Body temperature gradients [152]
long been known that temperatures
different parts of the body For e
the rectal temperature is usually a
mately 1° F above oral temperature
ever, if oral temperature be taken
much longer period of time, such as
utes, it more nearly approximates the
temperature

Body temperature gradients were
fully studied by Horvath and co-wo
The temperature of blood returning fr
brain and the liver was found to
proximately the same as that obtai
the rectum, but blood in the right
and, in particular, the superior ven
and the subclavian vein exhibited a
temperature These examples serve
phasize the fact that there exist s
cant variations between different p
the body with respect to temperatu
probably, heat production Therefore,
the rectal temperature generally aff
fairly reliable guide as to the di
which body temperature is taking, f
work is needed to evaluate the co
system of thermal gradients found i
normal person and in febrile states
example, in afebrile patients the av
difference between rectal temperatu
that of the right side of the heart
0 25° C but in febrile patients diffe

as great as 0 8 C were noted, the differences being even greater in patients with higher fevers.

Basal heat production The basal heat production is considered to represent the heat produced by metabolism in the individual who is resting both mentally and physically, and who is in the post-absorptive state The basal metabolic rate is usually measured, more or less satisfactorily, with the clinical BMR machine Actually, of course, this represents an indirect measurement of heat production since it utilizes only the oxygen consumed To measure heat production with accuracy, the individual can be placed in a Sage respiration calorimeter DuBois, Ebaugh, and Hardy[48] performed 76 experiments in the Sage respiration calorimeter on 13 normal young women at environmental temperatures ranging between 22 and 35 C The measurements in hourly periods included heat production, respiratory quotient, rectal temperature average surface temperature, total heat loss, conductance and the percentages of heat loss by radiation convection, and vaporization Careful note was made of muscle tensing, shivering, and sensations of cold, warmth and comfort. The average basal metabolism of the 13 women was 31 2 cal. per $m.^2$ per hour It was noted that this was so much lower than the heat production of men (per unit of surface area) that women have an advantage over men in the warm zones and do not need to sweat as much. In the cold zone some women but not all, lose heat less rapidly than men and are thus also more comfortable in a cold room

In the cold zone, the women studied lost about 67 per cent of their heat by radiation and this percentage dropped in linear fashion to zero when the calorimeter temperature was the same as skin temperature Vaporization accounted for only 16 to 18 per cent of the total heat loss at the coldest temperatures and reached the conventional values of 24 to 25 per cent only at environments of from 27 to 28 C

DuBois and his associates found that the comfort or neutral zone for women—naked and in strict basal conditions—extended from about 26 to 30 9 C In this zone the average skin temperature was 33 9 C, and in the upper part of the zone heat production closely approximated heat elimination Of the 10 women studied at temperatures of 28 C and below 6 showed an increase in metabolism greater than the amount which could be ascribed to muscle tension or restlessness This was considered evidence that some but not all women are subject to the "chemical regulation" of metabolism, though the amount of heat involved is small In the cold zone these workers found that the peripheral tissues lost so much heat that the average temperature of the body dropped 2 8 C before the onset of shivering The metabolism of the peripheral tissues would also fall with lower temperatures, therefore, since the total metabolism remained either constant or rose, it was concluded that there was an increase in the metabolism of the core of the body which compensated for the decrease at the periphery

Basal heat production varies with age, sex, height, weight, race, disease and/or state of nutrition. Although basal heat production has been better correlated with body surface area than with other indices, there is increasing evidence that the lowered metabolic rate of fat as compared with lean tissue helps explain the surprisingly "low" metabolic rates of obese individuals, where surface area is used for a yardstick

Ways of increasing basal heat production (*Fig 138*) Basal heat production can be increased in a great variety of ways. Among these are food intake with the specific dynamic action of foodstuffs and in particular protein, exercise anxiety hormonal imbalance as in thyrotoxicosis and pheochromocytoma, an increase in the environmental temperature trauma and pyrogens Moreover an increased body temperature may of itself further increase body heat production simply by the fact that heat increases the rate of most chemical reactions

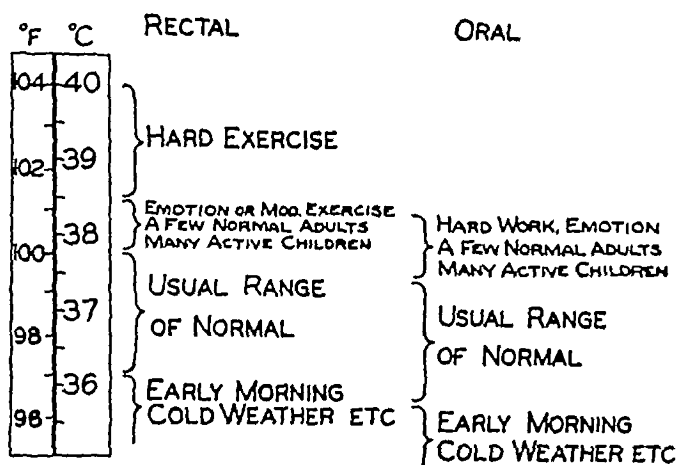


Fig 138 An estimate of the ranges of body temperature found in normal persons (From DuBois, E F *Fever and the Regulation of Body Temperature* Springfield, Ill, Charles C Thomas, 1948)

Mechanism of acclimatization It is of interest to consider the changes by which newcomers become better able to tolerate the heat of the tropics Extensive experiments during World War II revealed that the total blood volume of the individual tends to increase in warm climates and that the number of actively functioning sweat glands is increased A second type of adjustment is that the individual learns to wear proper clothing and to exercise with proper caution in the tropics It has not been found that the diet of persons in the tropics needs to vary greatly from that consumed elsewhere, though the intake of protein with its high specific dynamic action should probably be somewhat reduced

Fever

CLINICAL TEMPERATURE MEASUREMENTS Errors in clinical temperature measurements are often due to defective thermometers and to defective use thereof Dimond and Andrews[43] analyzed 465 clinical thermometers and found that a large percentage gave inaccurate readings at a standard temperature and that the error ranged from 0 5 to 3 3° F A second common cause of abnormal temperatures lies in the fact that the patient's temperature is taken by mouth after the consumption of hot or cold beverages, or after mouth breathing has cooled the oral cavity Rectal temperature

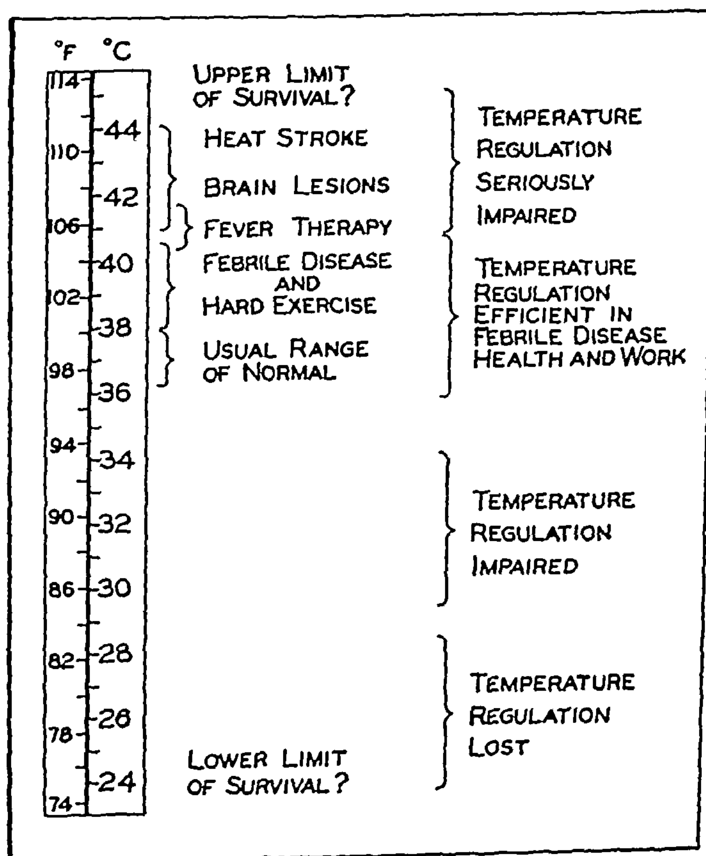


Fig 139 Extremes of human body temperature with an attempt to define the zones of temperature regulation (From DuBois, E F *Fever and the Regulation of Body Temperature* Springfield, Ill, Charles C Thomas, 1948)

measurements are more accurate than oral measurements. The occasional malingerer or practical joker may place the thermometer in hot liquid or upon the radiator and where such is suspected the nurse should remain at the patient's bedside for the entire time that the temperature is being taken. In shock, the oral temperature may be subnormal when the rectal value is high.

SOME CLINICAL FEBRILE STATES AND THE MECHANISM OF THEIR PRODUCTION. In Figure 139 are shown the ranges of body temperatures found in normal persons and the extremes of human body temperature, with an attempt to define the zones of temperature regulation. There may be a considerable range in the normal temperature of apparently healthy adults and in particular, children. Thus, a body temperature of 99 F in the surgical patient may or may not represent a low grade wound infection, thrombophlebitis, atelectasis of a pulmonary segment, or urinary tract infection. Moreover, it has been pointed out that a small rise in body temperature is a part of the usual reaction to operation.

Given below is a classification of different causes of fever which one may encounter in surgical patients, with an indication of the possible mechanism of the fever in each case. Since the processes of heat production and heat loss are closely integrated the mechanisms are probably never as simple as the following listings might indicate.

A. Fever due to increased heat production
   1. Psychogenic fever. This is due to emotional stress in children and, to a lesser extent, in adults (Fig. 140).
   2. Bacterial endotoxins and other pyrogens. It has been shown that this fever is due, at least in part, to diminished heat loss as well as to increased heat production.
   3. Thyrotoxicosis. The fever is due to an increased metabolic rate.
   4. Pheochromocytoma. Epinephrine and norepinephrine have a calorigenic effect.
   5. Certain tumors. Large goiters, hypernephromas, adrenocortical carcinomas, and tumors of the colon, among others, often produce fever, probably because of the liberation of necrotic material into the blood stream. "Sterile abscesses" may be encountered in the center of the mass.

B. Fever due to increased heat absorption
   1. Increased environmental temperature. This is particularly effective in a stressed individual who sweats less readily.

C. Fever due to diminished capacity for heat loss
   1. Trauma and stress with a diminished capacity for sweating. This is in part the cause of the common mild increase in body temperature following operation and anesthesia.
   2. Adrenocortical insufficiency. The fever here is probably due to diminished circulatory efficiency.
   3. Dehydration fever. This cause of fever has been exaggerated, but when it does occur, especially in infants, it is probably due to diminished circulatory efficiency.
   4. Heat stroke or heat exhaustion. This condition may be due not only to diminished circulatory efficiency but also to exhaustion of the sweat glands with resulting inability to dissipate heat normally by vaporization. However this condition is uncommon where increased heat absorption is not also present.
   5. Terminal shock. The fever is probably due to collapse of vascular conduction mechanisms.
   6. Cranial trauma. This probably affects the thermoregulatory center with its component reflex vascular mechanisms.
   7. Liver failure. Here the body temperature increase is probably due to diminished circulatory efficiency.
   8. Extensive sympathectomy. This reduces sweating, as do autonom

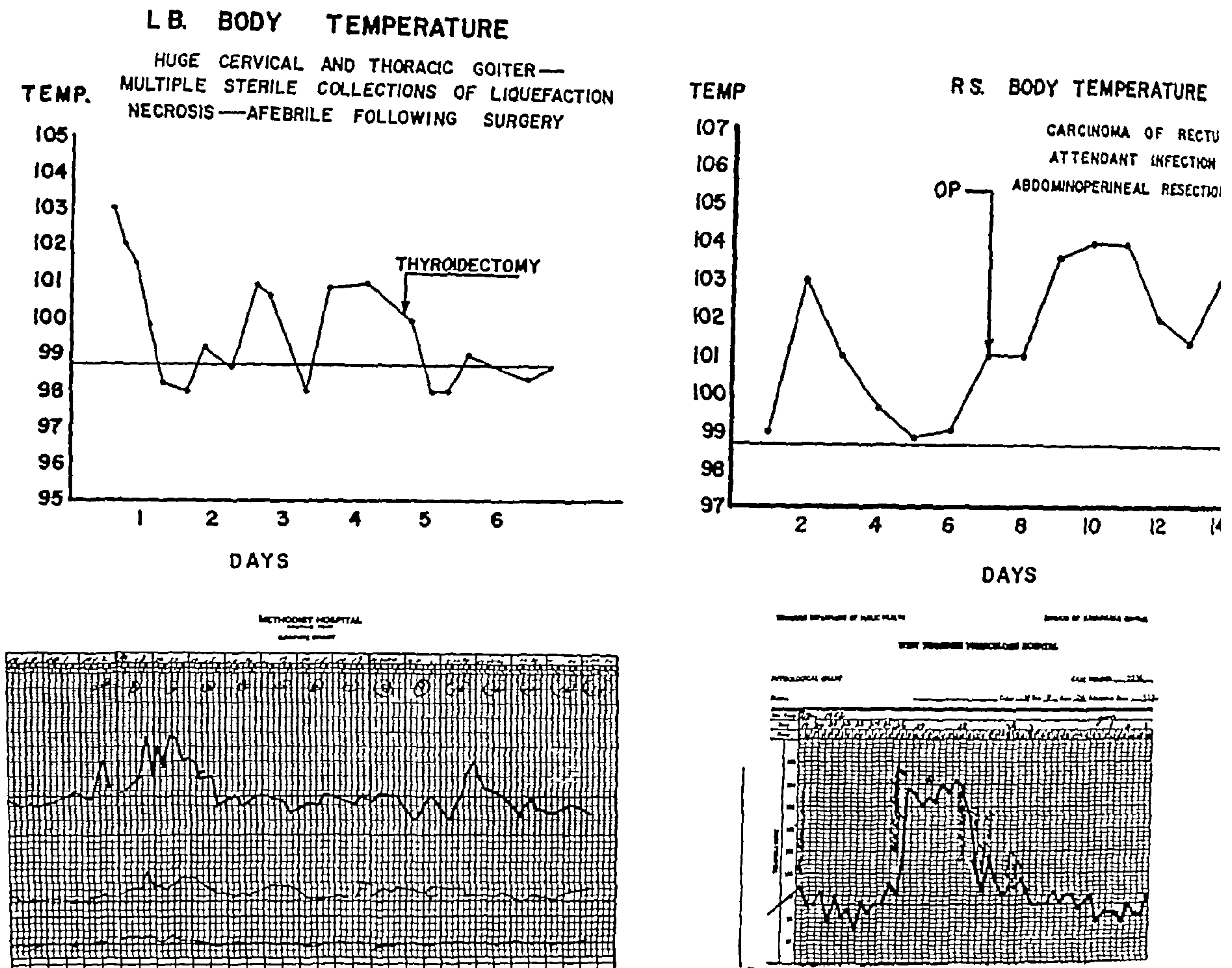


Fig 140 Upper left Fever due to absorption products of necrotic goiter *Upper right.* Fever due to infection and tumor necrosis The postoperative fever was not readily explained It persisted for several weeks *Lower left* Initial febrile episode was due to the stress of surgery for resection of coarctation of the aorta in this enormously obese young housewife The late spike was caused by anger when no one came to assist her back to bed Emotional crises may produce an elevated basal metabolic rate (BMR) that persists for several days *Lower right* Fever following resection of huge functioning right adrenocortical carcinoma The febrile reaction probably represented borderline adrenocortical crisis

blocking agents Exposure to excessive heat where sweating is the principal means of body heat dissipation may precipitate dangerous hyperpyrexia

9 Congenital absence of sweat glands Heat dissipation is defective

GENERAL DISCUSSION Although the above classification is brief and is offered only as a tentative guide, it is apparent that fever may result not only from an increased heat production due to increased body metabolism but also from a diminished heat loss This is particularly true in patients following trauma, for involved are psychic, neural, and chemical stimuli In a study of the alterations in sweat volume and electrolyte content in postoperative patients, we found that it was more difficult to obta sweat in a rubber glove after operation tha before operation It appeared probable th at least a part of the postoperative increa in body temperature in patients who did n have obvious infection or tissue breakdow was due to a diminished capacity to swe and thus to dissipate heat Similar result had previously been obtained in animals b Wells and Rall,[159] who studied the mecha nism of the increased body temperature fol lowing pyrogen-induced fever Even afte shivering and otherwise increased muscula tone had been abolished by curarization, th injection of the pyrogenic material still pro duced an increase in the body temperatur

of the animals, indicating that the fever was due at least in part to a diminished rate of heat loss Moreover, it was considered possible that the increased metabolism which resulted might be due in considerable measure to the retained heat which increased the rate of chemical reactions, rather than to the liberation of hormonal agents *per se* Whereas epinephrine has a calorigenic action the adrenocortical steroids tend to have an antipyretic action.

CASE STUDIES OF FEVER STRESS OF SURGERY, PSYCHOGENIC, MALIGNANT TUMOR AND ADRENOCORTICAL INSUFFICIENCY In Figure 140 are shown the temperature curves of 4 patients The first subject (lower left), who weighed almost 300 lb had undergone resection of a coarctation of the aorta There are seen two temperature spikes. The first episode occurred immediately after operation and was doubtless due to the stress of the procedure. The second spike, on the ninth day, occurred when the patient had been lifted out of bed into a chair but could then not get nursing assistance to get back to bed She became quite upset emotionally and the febrile episode was recorded during this time. Thus, the effect of operative stress is shown in addition to the development of psychogenic fever, the development of which was probably facilitated by the previous operative stress

The second patient (Fig 140 upper right) had a carcinoma of the rectum which had caused several minor episodes of fever prior to resection of the neoplasm The use of a hot drink and hot water bottles to produce sweating for sweat analyses resulted in a sharp rise in body temperature Moreover he later exhibited a much more marked febrile response to the operation than does the usual patient, perhaps because the additional stress was imposed upon an already stressed individual This case exemplified the fever that may be associated with a tumor the effect of operative stress and the diminished capacity of the stressed subject to adjust to external heat so as to prevent a rise in body temperature.

The third patient (Fig 140, lower right) exhibited the hyperpyrexia that may result from adrenocortical insufficiency An enormous functioning right adrenocortical carcinoma was resected and within hours the temperature was markedly elevated, due no doubt to inadequate replacement therapy, though she survived

The fourth patient (Fig 140, upper left) had fever due to sterile collections of necrotic tissue in a huge goiter

Of course, the commonest cause of significant fever in the surgical patient is bacterial infection whether in the wound or elsewhere Hyperpyrexia may also occur during anesthesia in the summer when the room is not air-conditioned, especially when the drapes are excessive Conversely when the patient under general anesthesia is exposed to low environmental temperature in an air conditioned room—as in the grafting of burn wounds—hypothermia may result. We have encountered rectal temperatures of 94 and 95 F in patients whose extensive granulating leg wounds had been uncovered for prolonged periods in an air conditioned room.

HYPERTHERMIA AND SURVIVAL. It is of both theoretic and practical interest to consider the extremes of body temperature that the patient can survive DuBois noted that in hospitals there are relatively few temperatures recorded which are above 106 F However, he and others have on occasion recorded much higher temperatures with survival of the patient, a recent one being the report by Fracchia and Brunschwig[37] of a woman who survived a brief period during which the rectal temperature was 114 F

Hyperthermia has long been used for certain therapeutic purposes It may be induced by heating cabinets, diathermy by the use of pyrogens such as killed typhoid bacilli or in other ways Such treatment was formerly used in the treatment of neurosyphilis since the patient could withstand the marked increase in body temperature but the spirochetes could not.

Hypothermia

ACCIDENTAL HYPOTHERMIA At least one nonfatal instance of a rectal temperature of 64 4° F (18 1° C) has been reported [97] The patient was found comatose in an alley during freezing weather On admission to the hospital the apical pulse rate ranged from 12 to 20 per minute, and the respirations were not at first detectable, though eventually a rate of from 3 to 5 per minute was noted The blood pressure was not obtainable in either arm at the time of admission The patient survived, but all four extremities had to be amputated

THERAPEUTIC HYPOTHERMIA [46] *The background* Although the clinical use of hypothermia has only recently been widely accepted, Smith and Fay[142] first introduced the technic in 1939 as a treatment for neoplasms Relief of pain promptly followed "refrigeration" of the area involved or induced states of "hypothermia" in which the patient was maintained at rectal temperature levels of 81 to 90° F for as long as 5 days In 1949 McQuiston[111] pointed out the dangers of hyperthermia in "blue babies," and in 1950 Bigelow[23] reported his important early studies in dogs which indicated that hypothermia might have wide application in clinical surgery For example, if by lowering the body temperature the oxygen requirements could be lowered significantly, exclusion of bloodless organs from the circulation for variable lengths of time would be possible It was demonstrated that when a dog's body temperature was reduced from 38° C to 20°C metabolism and oxygen requirements were reduced to approximately 18 per cent of their normal values Dogs under hypothermia survived occlusion of both venae cavae for 15 minutes, without brain damage Cooling produced a gradual fall in blood pressure, heart rate, and cardiac output to very low levels, with a reversal of these changes on rewarming Ventricular fibrillation was the most common serious complication and usually caused death at between 16 and 22° C

Parallel with these studies in Canada, important work was going forward in France, Great Britain, and the United States Laborit and Huguenard[96] employed their "lytic cocktail" (promethazine, chlorpromazine, and meperidine) intravenously to block the autonomic nervous system prior to surgery This "artificial hibernation" was induced to diminish the body's reaction to the trauma of surgery, permitting survival in poor risk patients It was felt that the incidence of shock was diminished Churchill-Davidson and his associates[37] concluded from their investigations that surface cooling was the simplest means available, general anesthesia being employed to reduce the reaction of the body temperature regulating mechanisms to the cooling process Swan[148, 149] and Lewis[100, 101] and their associates also conducted careful studies of the physiologic effects and clinical applications of hypothermia

The three technics most frequently employed for producing hypothermia have been various forms of surface cooling, extracorporeal circulation of the blood through cooling coils, and "artificial hibernation" by means of central autonomic blocking agents as advocated by Laborit Surface cooling is the method used clinically in most instances

Clinical comment Prior to cooling it is important, as stated, to achieve a level of anesthesia that will inactivate the temperature regulating center, to prevent the development of compensatory mechanisms such as increased muscle tonus and shivering which would increase oxygen requirements The principal risk of the induction of hypothermia is the incidence of *ventricular fibrillation*, especially after the heart has been exposed Hyperventilation to produce respiratory alkalosis and the injection of the sinoauricular node or of the auriculoventricular node with procaine have been used to reduce the incidence of ventricular fibrillation, with considerable success *Postoperative bleeding* is another serious complication, due to a reduction in platelets and probably to an interference with the enzy-

probably to an interference with the enzymic reactions required in the clotting process (Table 16)

Hypothermia has now been used in the management of a wide variety of clinical problems, but the most striking benefits have been in connection with surgery of the heart and aorta. Unquestionably, the further development of extracorporeal circulatory apparatus will diminish the use of hypothermia in cardiac surgery, since even with hypothermia the surgeon has a limited time in which to explore the opened heart and to repair defects, the pump-oxygenator will permit more leisurely and, hence, more meticulous corrective surgery for intracardiac lesions.

The Heart and Great Vessels *of the Thorax*

One could write a full length monograph on almost any of the multiple facets of the physiology of the heart and great vessels. In this review of the more immediately applicable material the objective has been to steer a middle course between information so new as to await a reasonable degree of confirmation, on the one hand, and that which has long been a part of established physiologic knowledge on the other Furthermore repetition of the commonplace data available in any standard textbook of physiology has been kept to a minimum compatible with clarity As in other sections, the purpose has been to present principles that are useful in clinical practice

Nervous and Chemical Influences upon the Heart

INTRINSIC INNERVATION AND CONDUCTION The chief nervous elements which regulate the heart beat and, in particular, synchronize the action of the atria and ventricles are shown in Figure 141 The heart (like the bowel) has important intrinsic nervous structures which are 'concerned with the initiation and propagation of the heart beat The more important of these are the *sinoauricular (S-A) node* the *atrioventricular (A V) node* and the *bundle of His*

TABLE 16 SOME PHYSIOLOGIC EFFECTS OF HYPOTHERMIA[46]

1 General metabolism and oxygen consumption —By hypothermia the oxygen requirements of a given tissue or of the entire body can be greatly reduced blood and tissue pH decline during hypothermia but this can be largely offset by hyperventilation of the patient
2 Respiratory system —Hypothermia leads to an increased anatomic dead space through bronchodilatation Spontaneous respiratory efforts are reduced in hypothermia but it is often difficult to determine the extent to which this is due to anesthesia Some manual or mechanical assistance is usually desirable during hypothermia
3 Endocrine system —Hormonal factors are of obvious importance in building up the fat which permits prolonged hibernation in animals The hypothalamus and its neuroendocrine connections appear to have a major rôle in controlling the onset and waking phases of hibernation In animals and in man hypothermia temporarily diminishes the release of adrenocorticotropic hormone (ACTH) by the pituitary the secretion of corticoids by the adrenal cortex, and epinephrine and norepinephrine by the adrenal medulla
4 Cardiovascular system —The blood pressure and pulse rate consistently decline in a fashion that roughly parallels the decline in the rectal temperature curve Systolic blood pressure levels of 80 mm Hg and pulse rates of 40 beats per minute are common at rectal temperatures of 28 C Myocardial irritability increases as the body temperature falls At rectal temperatures below 28 C ventricular fibrillation is a serious hazard. If it occurs, a normal rhythm may be difficult or impossible to achieve without rewarming the heart It is generally agreed that by maintaining the rectal temperature between 28 and 30 C the maximum benefit is derived from reduced oxygen requirements while avoiding undue risk of intractable ventricular fibrillation during cardiac surgery The circulatory changes observed during the induction of hypothermia are reversed in the course of rewarming
5 Blood coagulation —Serious coagulation defects are not infrequently encountered following hypothermia This may be due in part to the reduction in the number of platelets that occurs but doubtless other coagulation elements are defective also.

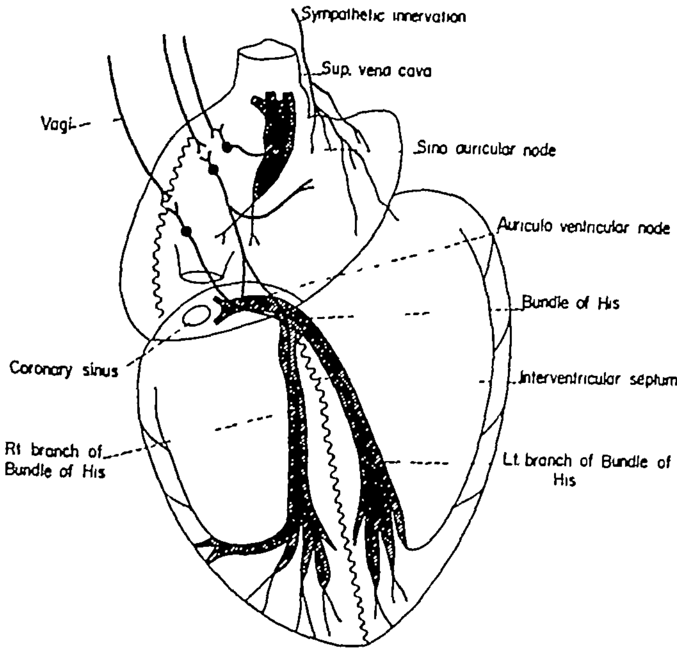


Fig 141 The cardiac conduction mechanism is readily injured in the closure of interatrial septal defects, especially the ostium primum types It is questionable whether the vagi extend to the ventricles

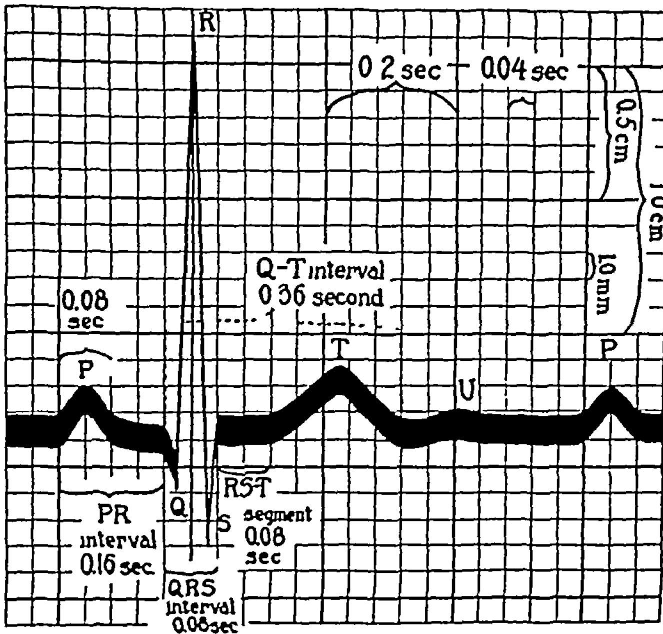


Fig 142 The normal electrocardiogram (From Ashman, R, and Hull, E *Essentials of Electrocardiography*, Ed 2 New York, The Macmillan Company, 1941)

with its two major branches which descend on either side of the interventricular septum The normal ECG is shown in Figure 142.

The S-A node, located at the point where the superior vena cava joins the free border of the right auricular appendage, initiat the heart beat and thus is called the *cardi pacemaker* It can be influenced by both l vagal and sympathetic impulses, of whi the former are clinically much more impo tant The practical clinical fact of curre importance is that the likelihood of ve tricular fibrillation can be reduced by bloc ing the S-A node with procaine,[128] a findi of particular value in hypothermia and op heart surgery

The A-V node is situated at the posteri and right border of the interatrial septu near the mouth of the coronary sinus Th position of this structure places it in jeo ardy when an interatrial septal defect being closed surgically by suture If th A-V node is injured, a serious and per haps total arrhythmia may result Webb showed that if the A-V node were injecte with procaine or divided, production of ven tricular fibrillation was almost impossibl

The bundle of His runs upward to th posterior margin of the membranous portio of the interventricular septum and then di vides into the right and left branch bundle (Fig 141) Damage to the several compo nents of this conduction mechanism is re flected in characteristic alterations in th electrocardiogram

Cardiac arrhythmias which are of specia and immediate importance to the surgeor are atrial fibrillation and ventricular fi brillation The former may be secondary to mitral stenosis, thyrotoxicosis, or hyper tensive-arteriosclerotic heart disease, or, n antecedent disease may be apparent Atria fibrillation *per se* reduces the efficiency of the heart, but much worse than this are the embolic complications of the arrhyth mia, among these are cerebral, mesenteric, and other arterial occlusions

Ventricular fibrillation is of course incom patible with life, for the ineffective and incessant uncoordinated movements of the ventricular muscle bundles produce no sig nificant cardiac output This arrhythmia may occur following myocardial infarction experimental ligation of a coronary artery,

during hypothermia, or when low blood oxygen or high blood CO_2 levels are permitted to occur during anesthesia. The management of this complication is considered in Chapter 17

EXTRINSIC NERVOUS AND CHEMICAL INFLUENCES *The vagus nerve* It has previously been stated that the vagal influence upon the heart is more important than the sympathetic influence. The vagal impulses exert a continuous modifying influence upon the heart rate, keeping the pace slower than if the intrinsic pacemaker—the S-A node—were unrestrained. This may be demonstrated by the administration of atropine

Acceleration of the heart rate in clinical circumstances is commonly due to an inhibition of vagal tone. For example, when the blood pressure falls the impulses arising in the carotid sinus (Fig 132) immediately travel to the vagal center in the medulla to suppress the vagal impulses and allow the cardiac rate to increase Clinically, a large variety of stimuli may by way of the cerebral cortex and the vagal center, result in an acceleration of the heart rate The heart rate may be increased directly, aside from vagal inhibition by the administration of epinephrine or stimulation of the sympathetic nervous system.

The *Bainbridge reflex* is also considered important in regulating the rate of the heart beat In brief, this reflex is activated when the venous inflow through the great veins to the heart is excessive and distention of the right atrium results. Nerve impulses are transmitted to the vagal center by way of an afferent limb of the vagus itself efferent vagal impulses are diminished and a more rapid heart rate is produced.

The sympathetic nerve fibers These fibers are less important in controlling the heart rate than is the vagus It is difficult clinically to separate the increased heart rate resulting from sympathetic nerve fiber stimulation from that caused by the simultaneous stimulation of the adrenal medulla which increases the production of epinephrine As with the vagus the center of sympathetic efferent nerve fibers is in the medulla oblongata. Of course, the sympathetic nerve fibers which accelerate the heart rate may be stimulated by a great variety of stimuli, among them being sight, sound, and other modalities.

Pain sensation from the heart is mediated largely, if not entirely, by the sympathetics, and the warning pain of angina is usually abolished by sympathectomy

There is believed to be a *cardiac center* in the floor of the fourth ventricle in the region of the vagal nucleus [161]

SOME CHEMICAL FACTORS INFLUENCING HEART RATE AND FORCE. Various chemical agents profoundly influence cardiac action. Although most of these have long been known it is only recently that they have come into clinical prominence due to the increased amount of cardiac surgery now being performed The more important of these will be considered

Oxygen and states of oxygen lack Oxygen is essential to life and nowhere else is this fact better illustrated than in connection with cardiac function. Hypoxia has a profound depressant effect on cardiac contractions and eventually, cardiac rate In the presence of oxygen lack, effective heart action is shortly replaced by cardiac arrest, either in standstill or ventricular fibrillation. *Defective oxygenation of the myocardium, often combined with hypercapnia, is the paramount cause of cardiac arrest during operation* especially *in the absence of* serious heart disease. This complication almost always reflects inadequate pulmonary ventilation—in the absence of shock due to blood loss or other physiologic deficiency

Carbon dioxide Young and his associates[162] published work to support their belief that hypercapnia (excessive concentration of CO_2) is probably a factor of considerable importance in initiating cardiac arrest during open chest operations. The increased CO_2 concentration was thought to increase the sensitivity of the heart to vagal stimulation with resulting cardiac arrest. Rather than representing a specific effect of the CO_2 molecule, the influence may be due to a reduction in the

blood pH In any event, one has merely to observe the decreasing rate and force of the heart beat in patients who are being poorly ventilated during open chest operations to develop a positive opinion regarding the rôle of hypoxia and hypercapnia in producing cardiac arrest

Potassium The potassium ion has an inhibitory effect upon the heart, and in sufficient concentration it will eventually cause cardiac arrest in diastole In general it is considered dangerous to allow the plasma potassium level to rise above 7 mEq per L, though the precise level at which serious cardiac depression will occur is influenced by the concentrations of other ions in the body fluids, particularly sodium, calcium, and probably magnesium Hyperpotassemia (hyperkalemia) produces characteristic changes in the ECG, and hypopotassemia produces other characteristic changes in the ECG However, the changes that have been produced by an elevated plasma potassium level may be alleviated if not abolished by the administration of sodium ion Thus, there exists a reciprocal relationship between the sodium ion and the potassium ion with respect to cardiac activity, as well as in many other physiologic circumstances

The fact that a sufficient concentration of potassium ion will produce cardiac arrest in diastole was utilized by Swan and associates[148, 149] in the treatment of clinical ventricular fibrillation Essentially, the aorta was clamped just distal to the coronary orifices, and a solution of potassium chloride was injected just proximal to the clamp and massaged into the coronary vessels to perfuse the myocardium We ourselves have used this ion in a 2 per cent solution experimentally, and it has produced cardiac arrest which could then be converted to a normal rhythm However, we have not used it clinically, preferring to use the defibrillating electric current The more potassium injected, the longer the heart will remain atonic before the potassium concentration in the myocardium has been diluted sufficiently to permit normal car[...] tivity Deliberate potassium arrest [...] used in open heart surgery

The clinical management of s[...] potassium excess or deficiency w[...] cussed in Chapter 2

Sodium An adequate concentratio[...] sodium ion is necessary for normal [...] function This may be due in large [...] the osmotic effect of sodium, which a[...] for the major osmolar effect in extra[...] fluid, but it also may be due to a [...] action of sodium ion, for there i[...] evidence that the various inorgan[...] have quite specific activities in [...] to their neutralizing and osmolar fu[...] It has been noted in a previous pa[...] that the sodium ion has an anta[...] effect to the influence of the potass[...] on cardiac activity, and that the del[...] effects of hyperkalemia can be dim[...] by sodium infusions

Calcium Whereas the administra[...] excess amounts of potassium ion wi[...] an inhibitory effect upon the hea[...] cause cardiac arrest in diastole, the a[...] tration of calcium ions promotes [...] creased strength of contraction of th[...] muscle and may eventually produce [...] arrest in systole The clinical appl[...] of this fact is that upon occasi[...] strength of an extremely weakened [...] beat may be increased, in the co[...] cardiac resuscitation, by the inject[...] calcium solution directly into the le[...] tricle or into the aorta just proximal [...] occluding clamp which will permit [...] sage of the injected calcium into th[...] nary arteries

The Physiology of Conditions which Surgery May Be Performed

Acquired Heart Lesions

ACUTE PERICARDIAL TAMPONADE [11] Th[...] common cause of pericardial tampon[...] a stab wound of the heart with resulti[...] mopericardium which produces compr[...] of the great veins as they enter the

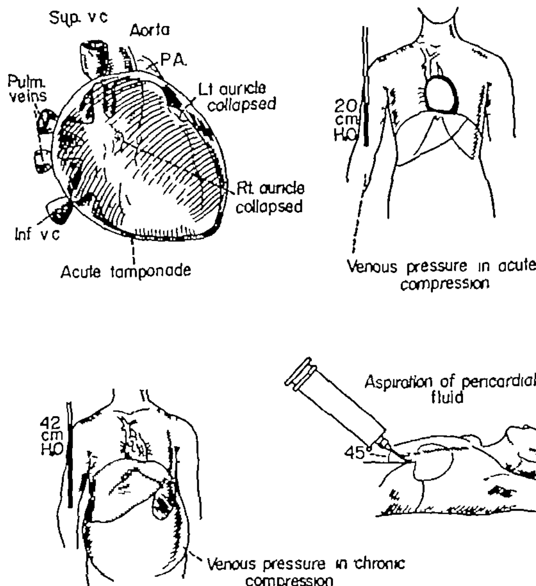


Fig 143 Acute pericardial tamponade and chronic constrictive pericarditis The atria and great vessels can withstand much higher intrapericardial pressures if these pressures develop slowly than if they develop acutely The pericardium is only slightly distensible in acute tamponade but *it can distend markedly in chronic effusions. Pericardiocentesis is* easily performed and may be lifesaving (After Beck.)

cardium Normally the pressures within the venae cavae and right atrium are somewhat less than atmospheric pressure This negative pressure within the mediastinum is produced in the same manner as is the negative intrapleural pressure, it ranges from −5 to −8 cm of water In chronic *pericardial compression the venous pressure* may be considerably higher than it is in acute compression before the same degree of disability is produced Under acute conditions however, serious reduction of cardiac output may occur when the pericardial pressure is between 10 and 15 cm. of saline solution. In other words, if the pressure upon the venae cavae and right atrium is increased by only a few centimeters of water, these structures are temporarily collapsed (Fig 143) The blood is dammed back in the great veins until sufficient pressure is built up to force the blood through the barrier of pressure caused by intra *pericardial* compression of the pulmonary veins and venae cavae. This compensatory increase in the venous pressure in the pulmonary and systemic veins has limitations however, and eventually the venous return to the right heart will be so inadequate that fatal shock will ensue. According to Beck the venous pressure within the right atrium

and venae cavae can rise to approximately 16 cm of water, but this can be considered the approximate fatal level for intrapericardial pressure developing acutely On the other hand, if the pressure develops slowly over a period of days or weeks, the venous pressure may rise to greater heights, even to perhaps 42 cm of water That is, as noted, over a period of time a high venous pressure can be built up that will serve as a protection against compression of the atria and great veins

The patient with acute pericardial tamponade due to a penetrating or perforating wound of the heart exhibits distended neck veins and a high venous pressure Beck[14] described the triad for acute compression of the heart as consisting of (1) a quiet heart, (2) a rising venous pressure, and (3) a falling arterial pressure It is also characterized by the presence of a paradoxical pulse Though the heart itself is smaller than normal because of compression by the blood in the pericardium, the cardiac silhouette is somewhat enlarged (though the fibrous pericardium is not readily distended acutely) Fluoroscopy reveals diminished cardiac excursions and shock may develop Furthermore, the patient may be alert one moment and in coma the next Conservative management with pericardial aspiration is virtually always indicated initially, not only as an at times lifesaving measure but also because it usually proves adequate

Case study A 39-year-old man was admitted in shock 2 hours following a penetrating knife wound in the left upper thorax anteriorly He was fully rational and the blood pressure was 90/70 An intravenous infusion of dextran was started, and he was taken quickly from the emergency room to the adjacent x-ray department for a film of the chest and cardiac fluoroscopy The cardiac silhouette was only moderately enlarged, but the cardiac pulsations were much diminished on fluoroscopy There was no evidence of fluid in the left chest By this time, however, the blood pressure had fallen to 60/40, and the patient was complaining urgently of a "smothering" sensation The neck veins had now become visibly distended, and the radial pulse was very weak Such an eventuality had, of course, been anticipated, and equipment had been secured to perform pericardial aspiration using a long 17-gauge needle and a 50-cc syringe (Fig 143) The needle was directed upward at a 45-degree angle just to the left of the xiphoid with the patient in the supine position No more than 30 cc of blood had been aspirated from the pericardial sac when the patient heaved a deep sigh and stated that he felt much better The distention of the neck veins disappeared as more blood was aspirated, and the arterial blood pressure rose promptly to essentially normal levels Meanwhile, a blood transfusion had been started and other blood held in readiness, should the pericardial aspiration prove inadequate and thoracotomy be required Actually, the tamponade did recur once and the pericardial aspiration was repeated several hours later Following this second tap there was no further difficulty, and the patient was allowed to go home after approximately 1 week

Comment The majority of patients with hemopericardium and tamponade can be satisfactorily treated conservatively by aspiration, repeated as necessary In the occasional case thoracotomy and myocardial suture must be resorted to, but this is rare, since patients with large heart wounds usually do not live to reach the hospital One possible complication of conservative management is that occasionally intrapericardial clotting will occur, and the resulting inflammation and fibrosis may eventuate in constrictive pericarditis Moreover, late refilling of the pericardium with blood and reaction fluid may cause rather acute compression after the patient has gone home For this reason it is important to follow these patients carefully for several weeks, including a chest x-ray and fluoroscopy immediately prior to discharge

CHRONIC CONSTRICTIVE PERICARDITIS *Etiology* A variety of pathologic conditions may produce the inflammatory changes in the pericardium and over the epicardium which result in chronic compression of the heart. Among these conditions are tuberculosis, pericardial empyema, hemopericardium, and uremia In many cases no definite etiologic agent can be identified but, of the last 5 patients that we have operated upon for this condition, 1 had proven tuberculosis 1 suppurative pericarditis following pneumonia, 1 chronic hemopericardium following a knife wound, 1 constrictive pericarditis of undetermined etiology, and 1 only a dilated heart due to heart disease (mistaken diagnosis) In subacute disease, the greatly thickened pericardium may contain a viscid exudate from which a fibrinous separate layer is deposited upon the epicardium. Not only the thickened pericardium but also the dense second "peel" overlying the epicardium must be removed at operation else the compressed heart will not be liberated (Fig. 144)



Fig 144 Patient S M Constrictive pericarditis following left lobar pneumonia and empyema Shown above is the heart from which both the thickened pericardium and the second dense inflammatory layer adherent to the epicardium itself have been excised Inspissated pus was contained in the pericardial sac If the pericardium and epicardium have not fused to form a single constricting layer the surgeon may conclude that excision of the pericardium is sufficient However not until the epicardial fat and coronary vessels have been identified is the heart adequately freed In fact the heart usually bulges through the window as it is progressively released

Diagnosis The chronic cardiac compression with chronically elevated venous pressure results in hepatomegaly, ascites, and edema The basic cause of the very obvious "heart failure" may not be immediately appreciated despite marked evidence of cardiac embarrassment

Since the condition has developed slowly, the pericardium has had time to enlarge. The fluoroscopic examination usually reveals diminished cardiac pulsations Calcium is frequently visible in the pericardium The ECG exhibits a diminished amplitude. The pulse pressure usually measures around 20 mm. Hg the systolic blood pressure ranges from 90 to 100 mm., and the pulse is paradoxical.

The *treatment* for constrictive pericarditis is radical pericardiectomy Our preference is first to make a left thoracotomy incision through which the diagnosis can be verified and the left ventricle and a portion of the right ventricle freed If all is going well at this point the incision is carried boldly across the sternum to achieve better exposure of the right ventricle, to attempt to remove the constricting material from a portion of the heart that is not well exposed is to court disaster from sudden and uncontrollable hemorrhage Again the fat of the epicardium should be exposed before the operator concludes that the decortication is adequate in depth, for the heart will literally bulge through when at last a window has been made in the constricting material Of 26 cases reviewed by Holman and Willett[83] 4 died though none from technical accident, 14 were considered to have nontuberculous pericardial thickening 8 patients had tuberculous pericarditis, and 1 patient did not have constrictive pericarditis but had a myocardial infarction It was concluded that, to be effective, pericardiectomy must be radical and, in order that all critical areas may be liberated the decortication must extend beyond the left border the right border, and the lower border with

release of both the inferior and the superior venae cavae at the base of the heart

We agree that an extensive resection is the desideratum, but much benefit can be achieved with a more limited operation, where required We were forced to terminate the procedure in one patient because of marked ventricular arrhythmia (monitored by cardioscope) Both ventricles had been adequately freed, but little had been accomplished over the base of the heart Yet, the patient appeared to be completely relieved postoperatively, whereas preoperatively he had progressed to almost fatal "heart failure" before the diagnosis of constrictive pericarditis was established

It is well to require a prolonged period of limited exercise postoperatively, before vigorous exertion is permitted The immediate success of pericardiectomy is best determined by the effect of the operation on venous pressure, and on the disappearance of edema and ascites when present The late results are best determined by the degree of rehabilitation of the patient

ISCHEMIA OF THE MYOCARDIUM Disease of the coronary arteries due to atherosclerosis constitutes perhaps the greatest health problem in the United States at this time Chronic narrowing of the lumen of these vessels may result, at first, in a diminished blood supply to the myocardium that is reflected in the symptoms of angina pectoris[131] If under these circumstances there should be superimposed upon the atherosclerotic narrowing an intraluminal clot or a subendothelial hemorrhage, the vessel may be closed completely, resulting in m cardial infarction of varying degrees (I 145) Coronary occlusion often occurs the first centimeter or so of the coron artery, just after it arises from the aor and ECG changes a ... ently diagnost While the immedi ... s in the EC may not be rem ... nite finding usually appear in ... The most common findings ... n in the RS-T segment with ... nverted

T-waves The Q-waves may be large Serial ECG's are of value not only in establishing the diagnosis initially but also in following the rate of healing, with the prognostic implications involved An ECG should of course be taken in any person suspected of having had a myocardial infarction, but it should always be remembered that "indigestion" and other symptoms of upper abdominal disease may in fact be due to coronary occlusion

Rôle of diet in coronary atherosclerosis There can be little question that there is a significant positive correlation between the fat content of the diet of a population and the incidence of coronary atherosclerosis It has been found that among certain African tribes and among the Japanese, where the proportion of fat to total calories in the diet is low, coronary disease is uncommon In contrast, in the United States, where the relative fat content of the diet is one of the highest in the world, the incidence of coronary disease is also one of the highest in the world It was formerly thought that the specific cholesterol content of the diet was the more important factor, rather than the total fat content, but this hypothesis is beginning to be abandoned in favor of the view that it is the total fat and caloric intake which predisposes to coronary atherosclerosis

Prior to the menopause, the incidence of coronary disease in women is much less than it is in men, but thereafter the incidence between the two sexes is more nearly equal Still further ... appears to be a ... ence in the i ... of coronary dis- ... in persons ... t occupations, whose occu ... ces them under uous ment ... more likely to coronar ... an those who al labor ... rative ... am U ... y, m ... of inj ... th ed d ... t

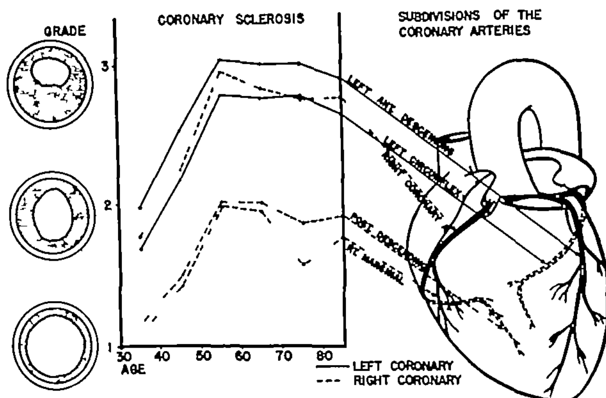


Fig 145 The most severe atherosclerotic lesions in each subdivision of the coronary arteries were determined in 100 consecutive postmortem examinations on men in each decade from 30 through 89 years. The average grade of the most severe lesion was plotted for each decade of life in each segment of the arterial tree Similar degrees of atherosclerotic changes were noted in the right main coronary artery and in the anterior descending and circumflex branches of the left coronary artery Smaller branches of the right coronary artery had less severe lesions Disease of the coronary arteries presents one of the major unsolved problems in cardiac therapy (From WHITE, N K., EDWARDS J E AND DRY T J The relationship of the degree of coronary atherosclerosis with age in men Circulation 1: 645 1950 as modified by RUSHMER, R. F *Cardiac Diagnosis A Physiologic Approach* Philadelphia, W B Saunders Company 1955)

sible that the impact of such surveys will eventually influence the composition of the American diet. However this is of no immediate help in the management of these problems. The prophylactic use of estrogen therapy in men who have had one episode of myocardial infarction must be considered entirely experimental at this time.

Operations for myocardial ischemia Direct surgery on the occluded coronary — Since arterial embolectomy or endarterectomy has been variously successful in other areas of the body it was natural to consider means of re-establishing blood flow through the occluded vessel, particularly since the occlusion very often occurs within a centimeter or so of the aorta. Bailey[4] has performed this operation in man but it must be considered highly exploratory thus far

Procedures to increase the vascularity of the myocardium —The several operations currently being used clinically and/or experimentally to improve myocardial blood supply are based upon the established fact that cross anastomoses between coronary vessels do occur (Fig. 146) Thus, the surgical procedures designed to enhance the blood supply of the ischemic area of the myocardium have as their physiologic basis the fact that a degree of retrograde flow

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Prior to the menopause, the incidence of coronary disease in women is much less than it is in men, but thereafter the incidence between the two sexes is more nearly equal Still further, there appears to be a difference in the incidence of coronary disease in persons of different occupations, those whose occupation places them under continuous mental stress are more likely to develop coronary disease than those who do manual labor with comparatively little mental strain Unquestionably, many other factors are of importance and these will be further revealed during the coming decades Meanwhile, certain large scale nutritional surveys are being continued, and it is pos-

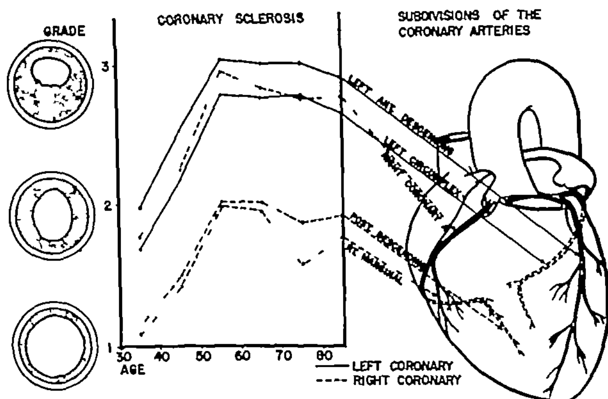


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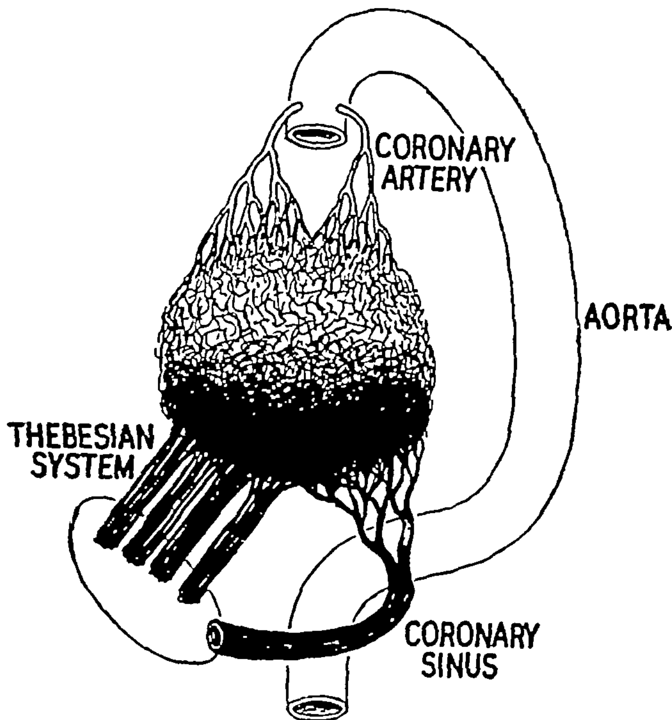


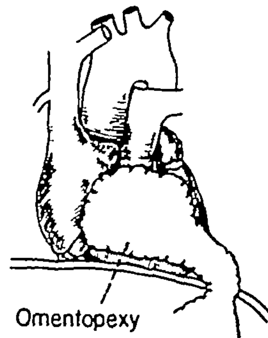
Fig 146 Concept of normal coronary circulation Shaded area represents capillary blood depleted of oxygen Efforts at myocardial revascularization are aimed at increasing the blood flow through coronary networks The Thebesian veins are usually less prominent than indicated above (From BAILEY, C P, GECKELER, G D, TRUEX, R C, LIKOFF, W, ANTONIUS, N A, ANGULE, A W, REDONDO-RAMIREZ, H P, AND NEPTUNE, W Arterialization of the coronary sinus J A M A, **151:** 441, 1953)

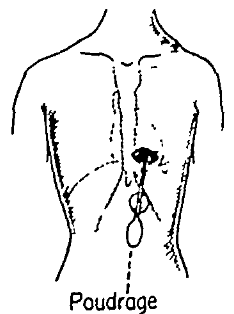
can occur among the coronary vessels While in normal young hearts less than 10 per cent of individuals have such anastomoses (the coronary arteries being, in effect, end-arteries) under various stimuli some anastomoses will develop to compensate for the relative insufficiency of oxygen, this is more likely to have already occurred in elderly individuals, where it was needed, than in younger persons In line with this is the belief that in the younger age group the prognosis following coronary occlusion is worse than in the older age groups, presumably since in the latter collateral channels have had an opportunity to develop (Fig 146).

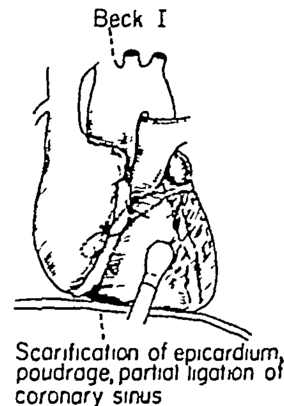
As early as 1936 it was demonstrated by Beck and his associates[15-18] and by O'Shaughnessy[118] that arterialization by the extracoronary methods could be accomplished Some of the tissues since used for *cardiopexy* have been muscle, fat, pericardium, lung, omentum, and the denuded seromuscular layer of the jejunum and of the stomach Thompson and Raisbeck[13] have had a particular interest in producing irritation within the pericardium by the instillation of iodinated talc (*poudrage*), with the objective of producing cross-anastomoses between the pericardium and the myocardium The success reported by different clinics using this method has varied widely, but at least it has the merit of both simplicity and a low operative mortality

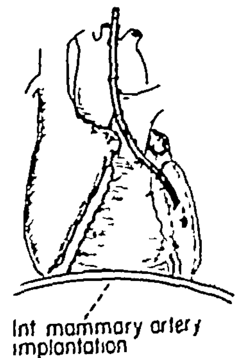
Arterialization of the coronary sinus is perhaps the most difficult operation advanced for revascularization of the ischemic

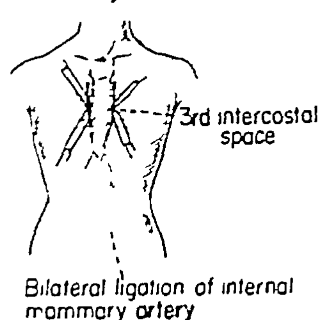
METHODS FOR REVASCULARIZATION OF THE MYOCARDIUM











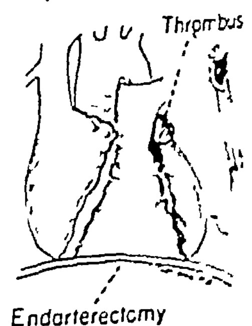


Fig 147 No consistently effective means of myocardial revascularization currently exists Poudrage is the simplest procedure, and for this reason it is most often used

myocardium. Proposed by Beck[17] and extended by Bailey,[7] it consisted of a series of steps by which a homograft was used to conduct aortic blood to the coronary sinus. This procedure gained few adherents and, as I have not used it, I do not feel qualified to evaluate it fairly

Systemic artery implantation was proposed by Vineberg[186] in 1946 Using the internal mammary artery, which was simply drawn into a tunnel in the myocardium without ligation, he and subsequently others demonstrated that buds from the implanted artery did anastomose with the coronary vessels. However, despite various refinements of technic, the clinical value of the procedure has yet to be securely established

General comment on revascularization procedures It must be admitted that none of the different operations mentioned above can claim consistent and unquestioned benefit in patients with coronary insufficiency The field remains wide open though with further use and refinement one or the other of the present technics may in the future prove more dependable than at present (Fig. 147)

DISEASES OF THE MITRAL VALVE. *Mitral stenosis.* Pathophysiology —The physiologic events attendant upon mitral stenosis result from increasing stricture of the mitral orifice over a period of years If the stenosis of the valve be corrected early enough irreversible changes in the myocardium and the pulmonary vascular bed will not have occurred and the patient can be largely rehabilitated On the other hand, if the disease is allowed to pursue its relentless course, a definite train of events may be observed at a variable rate of occurrence This train of events is approximately as follows [41] The obstructive lesion between the left atrium and ventricle has at least two major effects (1) it reduces the cardiac output and (2) it produces a rise in pressure in the system proximally—in the left atrium, pulmonary veins, pulmonary capillaries pulmonary artery and right ventricle (Fig. 148) Normally the

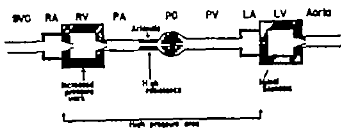


Fig 148 Diagram of the central circulation, showing the pathologic physiology of mitral stenosis. The pulmonary capillaries enjoy a wide differential between mean hydrostatic pressure (7 mm Hg) and colloid osmotic pressure (25 mm Hg) However if back pressure from the left atrium in mitral stenosis is sufficiently severe the capillary hydrostatic pressure may exceed colloid osmotic pressure and pulmonary edema then occurs Perhaps as a protective device mitral stenosis results in thickening of the walls of the pulmonary arterioles and increased arteriolar resistance This does protect the pulmonary capillaries, but it also increases the work load of the right ventricle and the pulmonary hypertension may produce cor pulmonale with eventual right heart failure (From DEXTER, L. Physiologic changes in mitral stenosis. New England J Med 254: 829 1956)

area of the mitral orifice is about 5 cm.^{2}, the pressure into the left atrium 5 mm. Hg and the cardiac output about 5 5 or 6 0 L. per minute. As the years pass, following one or more attacks of rheumatic fever, the size of the orifice diminishes, and critical narrowing occurs when the size reaches 1 0 cm.^{2}, a size at which all patients are symptomatic Paralleling the reduction in the size of the mitral orifice, the pressure in the left atrium has risen to a resting level of perhaps 25 mm. Hg at a valve size of 1 0 cm.^{2} and the cardiac output has declined to perhaps 4.0 to 4.5 L per minute The point of least resistance in the circuit is the pulmonary capillary, and the margin of physiologic safety before serious pulmonary edema develops is provided by the 25 mm. Hg pressure represented by the colloid osmotic pressure of the plasma proteins. Therefore as the hydrostatic pressure in the right atrium (and pulmonary capillaries) approaches 25 mm Hg the margin becomes so thin that the slightest emotion or exertion which increases the hydrostatic pressure in the pulmonary vessels may cause

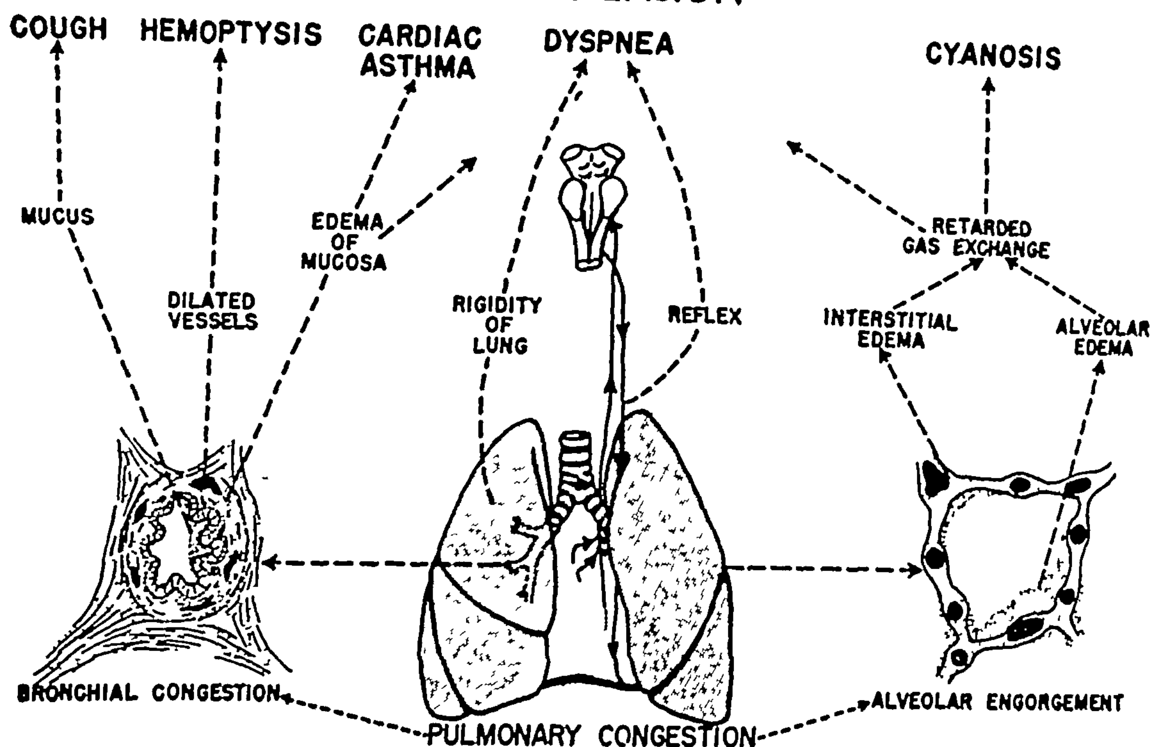


Fig 149 Since most bronchial capillaries drain by way of the pulmonary veins, congestion develops simultaneously in alveolar and bronchial vascular networks Bronchial congestion tends to stimulate production of mucus, leading to a productive cough The distended bronchial capillaries may rupture so that the patient has blood-tinged sputum (hemoptysis) Edema of the bronchial mucosa increases resistance to air flow, producing respiratory distress similar to asthma Dyspnea results primarily from reflexes initiated by vascular distention, but it may be aggravated by increased rigidity of the lungs and by impaired gas exchange resulting from interstitial edema and accumulation of fluid in alveolar sacs Cyanosis is not consistently observed even in patients with severe pulmonary edema Many mechanisms by which dyspnea is produced are still obscure (From RUSHMER, R F *Cardiac Diagnosis A Physiologic Approach* Philadelphia, W B Saunders Company, 1956)

transudation of fluid out of the vessels, evidenced by microscopic or gross pulmonary edema For this reason, dyspnea is a prominent symptom of mitral stenosis with pulmonary edema (Fig 149)

Pulmonary vascular changes occur late in the disease when the size of the mitral orifice is considerably reduced There is the thickening of the wall of the pulmonary arterioles, adding a second point of obstruction in the pulmonary circuit Dexter[41] has emphasized that it is the pulmonary hypertension which results from the increased arteriolar resistance (rather than hypertension due to stenosis of the mitral orifice) which produces enlargement of the pulmonary artery and right ventricle Teleologically, one might assume that the arteriolar thickening and increased vascular resistance, however produced, has the purpose of protecting the pulmonary vascular bed With the resistance in the lungs added to that at the mitral valve, a great burden is placed upon the right ventricle The pulmonary artery enlarges and the pulmonary arterial pressure, normally 25/9 mm Hg, may rise to or exceed that in the systemic circuit, pressures as high as 140 systolic and 75 diastolic have been recorded in the pulmonary artery The right ventricular pressure must exceed the pressure in the pulmonary artery, and the right ventricle will eventually fail (cor pulmonale) The cardiac output may fall to as low as 3 L or less per minute The left ventricle may diminish even below normal size, since the work it must perform is progressively reduced Again, if corrective mitral surgery

is performed early enough, most of these organic changes, including pulmonary arteriolar thickening, may be expected to regress.

Clinical findings.—The first *symptoms* which occur are usually related either to *dyspnea* or to an increasing functional incapacity related to easy *fatigability*. This may progress until even the slightest activity such as eating, dressing or going to the bathroom cannot be carried out by the patient without severe dyspnea and exhaustion. Later, atrial fibrillation perhaps embolic episodes pulmonary congestion and *hemoptysis*, and episodes of nocturnal paroxysmal dyspnea due to pulmonary edema may appear and eventually right heart failure may develop, with hepatic enlargement, ascites and dependent edema. In one series[137] heart failure of one type or another accounted for 44 per cent of deaths, acute events in the peripheral circulation (mainly embolic) for 33 per cent and pulmonary infarctions for 11 per cent—the other deaths being due to miscellaneous causes.

Diagnostic features of well developed mitral stenosis include the history of rheumatic fever, when obtainable plus the other symptoms outlined above. There are usually the typical apical diastolic murmur, and perhaps atrial fibrillation, pulmonary congestion and cardiac enlargement. *Roentgen examination* reveals increased pulmonary vascular markings pulmonary congestion and enlargement of the left atrium, the right ventricle, and the pulmonary artery. We particularly like to see the sharply defined backward displacement of the esophagus by the enlarged left atrium, which is well demonstrated by barium swallow in a lateral view. Left ventricular enlargement should be absent when present the probability of significant mitral regurgitation or aortic disease must be taken into account. The ECG frequently shows right ventricular strain. *Cardiac catheterization* while not required in the routine case, will show increased pulmonary arterial and capillary" or "wedge" pressures (the cardiac catheter being "wedged" into a small ramification of the pulmonary artery). Arterial oxygen saturation is usually normal at rest but may fall with exercise, as pulmonary blood flow and cardiac output fail to increase to meet the new demands. Representative data are shown in Table 17.

Indications for operation[8, 9, 63, 70].—A number of classifications of the degree of physical incapacity in mitral stenosis have been offered, but a general one which we use, is as follows: Group I, asymptomatic, Group II, definite symptoms, but exercise tolerance not seriously diminished. Group III, serious physical limitation precluding many accustomed activities, Group IV, severe limitation, marked evidence of cardiovascular failure and a bed patient, Group V, totally incapacitated and unsuitable for surgical treatment.

We reject for surgery those patients who merely have a mitral diastolic murmur but who have no symptoms of mitral stenotic disease. We do accept for operation those patients who have definite symptoms of mitral stenosis even though these may not be marked, since experience has shown that gradually most of these patients will develop additional symptoms and that meanwhile pulmonary vascular changes leading to pulmonary hypertension are occurring, not to mention the changes in the musculature of the overworked right ventricle. The longer that the patient has had symptoms of mitral stenosis, the greater the organic defects which have occurred and the less favorable the outcome following mitral valve surgery. Finally, we are now unwilling to operate upon patients who are all but moribund (Group V), for while the mitral obstruction may be relieved at operation, the operative mortality is high and the ultimate salvage is small. The operative mortality in Groups II and III should be less than 5 per cent.

Contraindications to surgery are active rheumatic carditis bacterial endocarditis, a significant degree of mitral insufficiency,

TABLE 17 CARDIAC CATHETERIZATION DATA IN MITRAL STENOSIS (PATIENT C B —♂—12 YEARS)

Site	REST				EXERCISE			
	Pressure (mm Hg)		Oxygen		Pressure (mm Hg)		Oxygen	
	S/D	M	Vol %	% Sat.	S/D	M	Vol %	% Sat.
Superior vena cava	—	—	11 81	57 53	—	—	—	—
Right atrium	—	±0	11 82	57 54	—	—	—	—
Right ventricle	64/9	19	12 16	59 22	—	—	—	—
Pulmonary artery	64/24	36	13 30	64 75	94/60	—	9 19	44 76
Pulmonary "capillary"	—	15	—	—	—	26	—	—
Brachial artery, right	127/83	93	19 24	93 70	—	—	19 32	94 10
Capacity	—	—	20 53	100 00	—	—	—	—

Discussion The end diastolic pressure in the right ventricle varied during the procedure from 2 to 9 The figure of 9 recorded above was the highest observed and is interpreted under the circumstances as evidence of no more than borderline right ventricular failure The pulmonary "capillary" pressure at rest is minimally elevated but rises sharply with exercise (and the exercise was not very vigorous) Pulmonary artery pressure is moderately high at rest The curve recorded during exercise was technically unsatisfactory so that its systolic level is uncertain, but the rise in diastolic level is marked

Conclusion There is moderate pulmonary arterial hypertension at rest and this increases with mild exercise While not diagnostic, the findings at catheterization fit well with the clinical diagnosis of mitral stenosis

This patient was greatly improved by valvulotomy An 0 8-cm (diameter) orifice was enlarged to from 2 0 to 2 5 cm (Catheterization data and critique supplied by Dr Thomas M Blake)

and intractable right heart failure (Group V) Serious aortic disease also complicates the picture, since the results of surgery for both aortic stenosis and aortic insufficiency leave much to be desired Aortic stenosis may be corrected at the time of mitral valvulotomy or at a separate operation

Each patient must be selected for operation on the basis of the total profile of his case Age *per se* is not a contraindication to operation, though generally many factors which militate against a good operative result will be present The oldest patient that I have operated upon personally was 52 years of age, and this patient was rehabilitated to the extent that, no longer bedridden on all drugs available, she was able to putter about in the flower garden, to drive her car, and to do light housework She was by no means completely normal, however Vigorous exertion produced dyspnea, and the atrial fibrillation could not be converted to normal rhythm with even massive doses of quinidine. Yet there were no embolic phenomena, and she was delighted with the results achieved by her operation

A very large number of operations for mitral stenosis have now been performed throughout the world, and the procedure (Fig 150) is securely established as a feasible and valuable source of relief for many patients who need it

Management of acute pulmonary edema —At the time of the induction of anesthesia the critically ill patient may suddenly develop fulminant pulmonary edema This is manifested first by pulmonary râles and increased tracheobronchial secretions However, this relatively benign situation may suddenly develop into severe pulmonary edema, with cyanosis, hypotension, and the frothy pink fluid which boils out of the endotracheal tube Unless treated expeditiously, this may terminate fatally Effective measures include elevation of the trunk, positive pressure oxygen breathing, and venous tourniquets on all four extremities If the patient is not already digitalized, this is ad-

visable Intravenous aminophylline may be helpful. Successful treatment produces a regression of the picture in reverse order the frothy pink fluid is replaced by a watery material and gradually the pulmonary râles recede.

Preoperative operative and postoperative emboli —One of the more distressing features of mitral stenosis with atrial fibrillation is the dislodgment of thrombi from the left auricular appendage, which pass into the systemic arterial circulation to occlude major arteries. While this is a particular hazard at the time of operation when thrombi in the left auricular appendage may be mobilized as the finger is inserted, embolization may occur any time As has been seen, most arterial emboli arise from the heart either as a mural thrombus secondary to myocardial infarction or from the left atrium in the presence of atrial fibrillation If the embolus involves the aortic bifurcation or an artery of the leg, embolectomy can be performed. Yet, while embolectomy *may be initially successful it is discouraging* how few patients are truly rehabilitated. The reason for this is that, first, embolization has occurred in a patient who already had a serious disease Second additional emboli often occur, even in the early period following removal of the initial embolus Therefore, while theoretically embolectomy should prove to be a very satisfactory operation either the patient or the leg is often lost.

Postcommissurotomy syndrome [45]—Following surgery for mitral stenosis a variable number of patients have precordial chest pain fever and sometimes cough with or without evidence of pleurisy and pericarditis. The pain, which is the most prominent feature may cause much disability This condition has come to be known as the 'postcommissurotomy syndrome The time of onset of the condition ranges from a few days to months following operation, and after persisting for from 10 to 30 days it gradually subsides. The syndrome has been

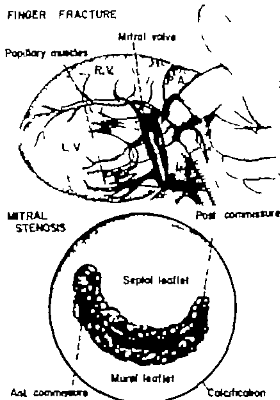


Fig 160 The stenotic mitral orifice does not have to be greatly enlarged to provide marked relief though it should be opened adequately

variously attributed to reactivation of the rheumatic process, to traumatic pericarditis, or other causes The symptomatology gradually subsides spontaneously, but the use of salicylates and/or cortisone has seemed to provide symptomatic relief

Hemorrhage at operation —I have twice encountered severe hemorrhage at the time of valvulotomy In the first instance the hemorrhage occurred when, as the assistant drew up firmly on the purse-string suture, the atrial appendage tore just proximal to the purse-string suture at the base posteriorly One hesitated to place a deep mattress suture lest the pulmonary venous return or the left coronary artery be occluded However, after considerable blood loss (and exasperatingly ineffective effort) the atrial appendage was turned down and sutured over the defect in the groove and to all appearances, the bleeding was controlled Accordingly, the chest was closed. Unfortunately, as the patient emerged from the anesthetic he became violent and pres-

ently, the water in the closed drainage bottle began to turn pink from fresh hemorrhage, and after several transfusions it was judged essential to re-explore the pericardial cavity. As anticipated, a slow but steady stream of blood was flowing from the sulcus between the atrial appendage and the left ventricle. The previous tear was exposed, but at this point cardiac arrest occurred. Between periods of cardiac massage the defect was boldly sutured securely with two mattress sutures but, though heart action was restored, the strength of contraction was not good and the patient died an hour or so later.

The second instance of hemorrhage was readily controlled on the basis of the experience gained with the first. In the second case hemorrhage occurred when, while pressing against the anterolateral commissure perhaps too firmly, in an effort to fracture it in the presence of considerable calcification, a calcified plaque appeared to act as a bayonet, stabbing a hole in the lateral wall of the atrium just above the atrioventricular groove. This time, however, the finger was kept in the atrium and the tear was occluded *from the inside*, by simply bringing the distal phalanx against the lateral atrial wall. This simple maneuver virtually stopped the bleeding, and closure of the defect over the finger was readily accomplished under direct vision.

While undoubtedly most experienced surgeons will have decided upon their own measures for the control of such unfortunate accidents, I consider it highly desirable to keep the finger in the auricular appendage or to reinsert it promptly to assist in controlling the hemorrhage by gentle compression from the inside, permitting direct inspection and suture of the laceration. If it is in deep in the sulcus between the atrial appendage and the atrium, the atrial appendage can be sutured as a flap for tamponade. If the defect is between the atrium and the ventricle, the atrial appendage can be brought down and sutured to the wall of the ventricle as a flap. Since the pressure within the atrium is relatively low, such measures will usually control the hemorrhage. Above all, the most important single feature is for the surgeon not to become panicky and to avoid injudicious haste in inserting deep sutures. If a suture is not so placed as to occlude the circumflex coronary artery or the pulmonary veins, adequate blood transfusion and care in meticulously controlling the hemorrhage will usually allow the surgeon to recover from this otherwise catastrophic predicament.

Finally, gentleness is so very important in the approach to the mitral valve. Poise and precision are achieved here, as in other surgery, only through experience.

Mitral insufficiency. Pathophysiology of mitral regurgitation.—Mitral insufficiency results from two principal defects: (1) an absolute loss of substance and (2) a relative loss of substance.[2] The *absolute loss* of valvular tissue comprises the basic form of regurgitation wherein the disease process (usually rheumatic) has attacked the leaflets directly and the resulting contracture prevents their closing in systole. A *relative loss of substance* occurs either as a result of rheumatic carditis which attacks the valve annulus directly or because of generalized left ventricular dilatation secondary to myocardial disease and failure. As the annulus enlarges, the valve leaflets, otherwise adequate in length, fail to approximate and regurgitation results. This type of regurgitation includes those forms of incompetence often referred to as "functional insufficiency." Shortening of the papillary muscles and chordae tendineae also precludes ideal elevation of the leaflet margins to permit perfect closure during systole. Also, by improper valvulotomy the mitral leaflet may be detached from its chordae tendineae and papillary muscle support and flap to and fro with the blood current in systole and diastole. Or, the mitral leaflet may be divided in the center rather than at the commissure, as was deliberately done in the early attempts at surgery for mitral stenosis many years ago. Nevertheless, this

is an artificial type of mitral insufficiency, and is not the pattern observed in the naturally occurring disease. As stated, the most common type of mitral regurgitation undoubtedly occurs due to the inflammatory reaction of rheumatic carditis which results in scarring, shortening, and contracture of leaflets and chordae tendineae, thus making it impossible for the valve margins to approximate.

Cardiodynamics in mitral regurgitation are such as to increase the work of the left ventricle. With each systole a considerable volume of blood, which varies in amount with the degree of valvular incompetency, is regurgitated into the left atrium, in addition to the ejection of blood into the aorta. This has been beautifully demonstrated with cine-roentgenography. As left ventricular hypertrophy occurs to compensate for the effort wasted by the backflow of a variable amount of blood into the left atrium with each systole, there is a further enlargement of the mitral valve ring with further incompetency, due to a relative deficiency in the amount of valve leaflet surface available for covering the now further enlarged mitral area. Thus a vicious cycle is produced which must eventually lead to heart failure if sufficiently severe.

Diagnosis of mitral regurgitation — While there is as yet no satisfactory surgical method of treating mitral regurgitation, it is of much practical importance to be able to diagnose mitral regurgitation, since the presence of significant mitral insufficiency may render operation for mitral stenosis inadvisable. Patently, if a marked degree of regurgitation exists, stenosis cannot be great. Abelmann, Ellis and Harken[3] studied 64 patients with a view to establishing dependable criteria for the diagnosis of mitral regurgitation. Particular note was made of the following: the apical systolic murmur, the symptom of easy fatigability, enlargement of the left ventricle, absence of the electrocardiographic pattern of right ventricular enlargement or right bundle branch block, marked enlargement of the left atrium, systolic expansion of the left atrium as assessed by fluoroscopy, the atrial esophagogram, the atrial border electrokymogram, and the phonocardiogram. They found that the most dependable criteria for the diagnosis of marked mitral regurgitation were the presence of a loud apical systolic murmur, marked left atrial enlargement, left ventricular enlargement, and systolic expansion of the left atrium by fluoroscopy. Their findings with regard to the value of apical murmurs were particularly enlightening, especially as it has been appreciated for some time that a diagnosis based purely on murmurs is likely to be erroneous in a certain number of cases. They found that of 14 patients with systolic apical murmurs of Grade 3 or louder, 6 showed severe regurgitation at operation, 4 showed mild to moderate regurgitation, and *4 showed no regurgitation*. On the other hand, of 23 patients without systolic murmurs, there was no regurgitation in 15, it was questionable in 7, and it was moderate in one. With respect to left atrial enlargement of 9 patients with marked regurgitation, 6 had markedly enlarged left atria and 3 had moderate enlargement only. Of 45 patients with slight or moderate enlargement, 29 had pure stenosis, 13 had questionable to moderate regurgitation, and only 3 had marked regurgitation. Abelmann and his associates[3] found that fatigability overshadowed dyspnea as a principal symptom in mitral regurgitation, in contrast to the dyspnea usually associated with mitral stenosis. It was concluded that no single criterion presently available is adequate for the absolute preoperative diagnosis of the degree of mitral regurgitation in patients who also have mitral stenosis. Direct *left atrial puncture*[27] and cinefluoroscopy will probably be rendered more practicable and informative procedures. Yet, as noted, it was possible to determine with considerable accuracy clinically the probable pathology, which was later verified at operation. The presence of a systolic murmur of Grade 2 or less, a left atrium moderately enlarged

in the posterior direction only, evidence of right ventricular enlargement on roentgenogram or ECG without evidence of left ventricular enlargement, and the finding of definite but slight systolic posterior expansion of the left atrium by fluoroscopy, kymogram, or esophagram suggest that mitral insufficiency of a degree to contraindicate cardiac surgery is not present On the other hand, definite evidence of left ventricular enlargement associated with other presumptive signs of mitral regurgitation—such as a loud systolic murmur, marked left atrial enlargement with systolic expansion, and fatigability rather than dyspnea—is suggestive of mitral insufficiency advanced to the point as to render exploratory cardiotomy inadvisable

Operations for mitral insufficiency —As previously noted, no satisfactory operation for mitral insufficiency exists at the present time Various workers have investigated the use of a heavy purse-string suture introduced around the annulus but not entering the atrium, but this and other procedures for mitral insufficiency must be considered experimental Repair under direct vision may become practicable and is being explored

Aortic stenosis Pathophysiology —Of all the valvular defects, aortic stenosis is one of the most intractable to conservative management Bergeron and co-workers[21] studied 100 patients with aortic stenosis who had come to autopsy They found that left ventricular failure and atrial fibrillation were grave signs and that, particularly when these were followed by cardiac pain or syncope, death usually occurred within weeks or months Of 34 patients to whom surgery was recommended but was not accepted, 30 were dead within 6 months

Aortic stenosis is usually due to rheumatic disease but may occasionally be of congenital origin or due to arteriosclerosis in elderly persons It results in obstruction to the outflow of blood from the left ventricle, with consequent hypertrophy of the left ventricle and eventual heart failure Bailey and his associates[5] believed that the reason for the poor response of aortic steno[s] medical therapy—as compared with th[e] sponse of other lesions—was to be expl[ained] on the basis of the mechanism of coro[nary] artery filling and flow, coronary filli[ng] often impaired in the presence of a[ortic] valvular disease Moreover, the greatl[y in]creased bulk of the overworked left [ven]tricle also limits the success of conserv[ative] therapy And the progressive narrowin[g of] the stenotic orifice further imposes [addi]tional limitations upon the advantages [to be] gained from medical management Fin[ally] many of the patients with aortic ste[nosis] are in the older age group beyond 45 y[ears] of age, in whom changes in the myocar[dium] and the coronary vessels would be expe[cted] to occur more frequently Neverthe[less] aortic stenosis due to rheumatic cha[nges] may occur in much younger persons, [with] the same relentless progression to deat[h]

Surgical correction of aortic stenosi[s] The first attempt at operative correctio[n of] a valvular lesion in a human being [was] made upon a stenotic aortic valve by T[uf]fier[154] in 1913, when he successfully digit[ally] dilated a stenotic aortic valve by invagi[nat]ing the anterior flaccid aortic wall. In [this] way he was able to avoid a direct oper[ation] into the lumen of the cardiovascular syst[em]

In current efforts toward the relief [of] aortic stenosis a variety of attacks are [be]ing examined Bailey and his associa[tes] reported a relatively large experience w[ith] this condition, including approaches thro[ugh] both the aorta in a retrograde fashion (p[re]ferred) and through the wall of the [left] ventricle By the aortic approach, splitt[ing] of one or more of the fused commissures [by] simple finger pressure was possible in [al]most one-half the patients, whereas inst[ru]mental aid was required in the rest. M[ore] recently, various workers have utilized h[y]pothermia and attacked the stenosed va[lve] under direct vision The pump-oxygena[tor] is also being utilized to permit leisurely a[nd] yet more precise reparative surgery un[der] direct vision

The *results of aortic valvulotomy* ha[ve]

been far less favorable than those following mitral valvulotomy, though with further experience and diminishing mortality rates *this disparity may be reduced.*

Aortic insufficiency Pathophysiology —The basic pathology of aortic regurgitation consists of damage to one or more of the aortic cusps by rheumatic endocarditis, lues, trauma, congenital defects or bacterial endocarditis. The volume of regurgitation varies widely between patients and this is an important consideration in evaluating the *prognosis* in the individual case The patient with aortic insufficiency may, of course, have other valvular lesions, one of the more common being mitral stenosis

The patient with pure aortic insufficiency may die from cardiac decompensation secondary to the increased work imposed upon the left ventricle in delivering the required amount of blood to the tissues since much effort is wasted as a portion of the blood flows back into the ventricle through the incompetent aortic valve during each diastole. Or, the patient may die very suddenly from ventricular fibrillation caused by inadequate coronary flow *Many of the patients* will have evidence of angina pectoris, and in a large number there is a loud systolic murmur at the apex (in addition to the basal diastolic murmur) which may be suggestive of mitral insufficiency When Hufnagel[94] had an opportunity to examine at autopsy patients who had had a loud systolic murmur in the presence of aortic insufficiency it was *usually found that there* was enlargement of the mitral valve ring secondary to enlargement of the left ventricle

Gorlin and Goodale[44] emphasized the *value of serial blood pressure recordings* in the detection of incipient heart failure in aortic insufficiency The appearance of a narrowing pulse pressure was considered the alert for intensification of all therapeutic possibilities in view of the grave prognosis once congestive heart failure becomes established in aortic insufficiency

Operations for aortic insufficiency —Of the several operations which have been at*tempted for the relief of aortic insufficiency,* among them the insertion of an aortic homograft the only one which has enjoyed even reasonable success has been the insertion of the aortic valvular prosthesis of Hufnagel In brief this procedure consists of inserting into the upper descending aorta a plastic tube containing a ball valve The force of the systolic rush opens the valve, *and the diastolic backflow along the thoracic* aorta closes the valve (Fig. 151)

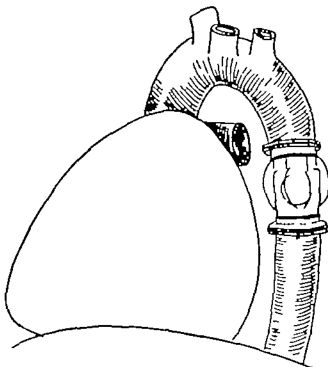


Fig 151 The Hufnagel valve has *proved to be* of much benefit in some patients who otherwise would have died within months.

Physiologic effects of the Hufnagel valve [120]—The therapeutic objective of the Hufnagel operation is to reduce the *volume of blood* regurgitated into the left ventricle which would of course diminish its work load. On the other hand a deleterious effect of the operation is to diminish the coronary artery perfusion pressure in these patients, since in diastole the valve (located *distal* to the coronary orifices) prevents backrush of blood from the lower portion of the body Thus, the patients who

are improved by the operation presumably enjoy a decreased workload of the left ventricle which is relatively greater than the diminished perfusion pressure of the coronary vessels, as a result, relatively more oxygen is available to the myocardium Organ perfusion is increased On the other hand, those patients who are made worse by the operation would presumably be those whose coronary perfusion pressure (and oxygen supply to the myocardium) was relatively more diminished than was the work load of the left ventricle In short, the Hufnagel operation represents a "physiologic gamble"

Following the Hufnagel procedure there often develops a degree of anemia which may be serious It is particularly so when one remembers that any degree of anemia will be poorly tolerated by a myocardium whose blood supply is already limited by the diminished coronary perfusion pressure caused by the aortic valvular insufficiency It has been suggested that the "sudden death" which occurs approximately 7 to 8 days following the Hufnagel operation in some patients is actually due to the diminished hematocrit which often occurs by this time When coronary insufficiency is present, degrees of anemia which are normally well tolerated may seriously impair ventricular function and a comparable situation exists in patients with aortic regurgitation

Hufnagel[84] reported patients, previously incapacitated, who had survived his operation for 3 years The immediate mortality of operation was 20 per cent and the death of an additional 20 per cent was anticipated within the following 2 years Yet, many patients had been able to carry out a relatively normal routine postoperatively Our experience with only 3 patients has been encouraging

While no one would claim that the plastic valve has solved the problem of aortic insufficiency, the important fact is that the feasibility of such an operation has been demonstrated Open repair will come

Congenital Heart Lesions

It has been the common practice to divide congenital heart conditions into "cyanotic" and "acyanotic" groups However, the importance of such a descriptive classification has seemed to us to recede somewhat as physiologic data have become available from cardiac catheterization studies Moreover, certain defects that do not produce cyanosis at one stage may do so at a later stage For our purposes here, let it suffice to state that, in the absence of heart failure, conditions which permit a sufficiently large shunt from the right heart to the left heart will be associated with cyanosis, while those which produce a left to right shunt will not be associated with cyanosis The direction in which blood flows through a shunt or defect is governed by the relative pressures on the two sides of the defect

The management of congenital heart disease has become a highly specialized and refined field of endeavor, and accurate evaluation by a dependable group of pediatricians and cardiologists is virtually indispensable for the conduct of successful surgery in congenital heart disease The diagnostic aids are the history and physical examination, electrocardiogram, plain roentgen films and angiocardiography and, highly important, cardiac catheterization

The presence or absence of *cyanosis* is still of much diagnostic assistance in the management of congenital heart disease For the patient to exhibit the bluish color imparted to the skin by the presence in the capillaries of more than 5 gm of reduced hemoglobin per 100 cc of blood, there must usually be a right to left shunt, that is, there is a passage of blood from the right heart or pulmonary circuit directly into the systemic system, bypassing the pulmonary capillaries where the blood escaping through the shunt would normally be oxygenated Certain congenital heart lesions are rarely associated with cyanosis, whereas other lesions are usually associated with cyanosis Of course, a left to right shunt—one from

the left heart or systemic circulation to the right heart or pulmonic circulation—would not produce cyanosis, since blood already saturated with oxygen is being 'wasted' into the pulmonary circuit. Yet, the oxygenated blood thus shunted will impart a higher than normal degree of oxygen saturation to the blood in the vessel or chamber to which it flows, a fact which can be established by gas analysis at cardiac catheterization and which is of aid in diagnosis. Tetralogy of Fallot is the commonest congenital heart lesion that produces cyanosis.

As just indicated, the term *shunt* is usually employed to describe an abnormal flow of blood that short-circuits the regional capillary bed. For example a pulmonary A V shunt allows unsaturated blood from the pulmonary artery to pass directly into the pulmonary veins, without first passing through the pulmonary capillaries to be oxygenated. A right to left shunt in the heart bypasses the pulmonary capillaries, a left to right shunt in the heart bypasses systemic capillaries. Of course A V shunts may occur anywhere in the body (Fig 174). The *direction* that the blood flows through a shunt is again determined solely by the pressures on the two sides.

Murmurs are important in the diagnosis of acquired valvular heart disease but even more so in congenital heart disease. In the first place, it is usually a murmur (or cyanosis, e.g. "blue baby") that brings the heart lesion under study for diagnosis and treatment. A murmur is a sound produced by the rush of blood through an aperture that is in some way abnormal. Some murmurs have such distinctive and characteristic qualities that they represent the keystone of diagnosis, particular ones being those of mitral stenosis and patent ductus arteriosus.

Angiography is the term applied to the injection of radiopaque material into blood vessels for roentgen visualization. Such *study of the heart is called angiocardiography.* Angiography has been employed for visualization of virtually all the important vessels of the body.

Cardiac catheterization consists of the *passage of a catheter through an antecubital vein, into the right atrium, right ventricle,* and thence into the pulmonary artery, if no shunt allows it to pass elsewhere. Measurements of blood oxygen saturation in each chamber can be made from blood samples withdrawn through the catheter, cardiac output can be determined by the direct Fick principle (including estimates of the volume of flow through various shunts), and pressures can be recorded in the accessible chambers of the heart by means of *sensitive recording devices.* The left side of *the heart is not readily accessible to catheterization unless an interatrial or interventricular* septal defect exists, though recently needles have been introduced directly through the posterior chest wall and into the left heart for pressure studies. With pressures and blood oxygen saturation values available, the diagnosis of various lesions can be made.

PATENT DUCTUS ARTERIOSUS. The patent ductus arteriosus is an important part of the fetal circulation (Fig. 127) for it permits a portion of the blood pumped by the right ventricle into the nonaerated lungs to pass from the pulmonary artery into the aorta. At the time of birth or within the first 2 days thereafter this *shunt usually closes by a process that is poorly understood (see p 632), and separates the pulmonary circulation from the systemic circulation.* In *the occasional individual this vessel does not close and* in effect, an arteriovenous fistula (p 447) remains. Since the shunt is from the aorta to the pulmonary artery, there is no cyanosis in the usual or uncomplicated case. Curiously, the incidence of this defect is greater in girls; in a series of 525 patients treated surgically by Gross,[64] 70 per cent were females.

Clinical and diagnostic features. Although these children may show some retardation of growth, generally the abnormality is well tolerated during childhood and cardiac de-

compensation is not frequently observed in this age group There is no mental retardation The most common finding which brings the patient to the physician is the discovery of a heart murmur at the time of a routine physical examination, often at school The murmur is the most characteristic finding, is heard best in the second or third interspace to the left of the sternum, and usually is present throughout the cardiac cycle The systolic component is preponderant in most cases, and in the occasional subject no diastolic component is heard The absence of the diastolic component, which occurs in perhaps 5 per cent of cases, is an indication for cardiac catheterization to rule out atrial septal defect or isolated pulmonic stenosis The pressure in the pulmonary artery and its oxygen saturation would be elevated by the shunt of completely oxygenated blood from the high pressure aorta to the low pressure pulmonary artery At times the catheter may pass directly from the pulmonary artery, through the defect, and into the aorta However, the characteristic murmur is—with collateral clinical data—diagnostic in perhaps 95 per cent of cases

Although the patent ductus may not give rise to symptoms during childhood, it should not be looked upon as a benign lesion The partial transmission of aortic pressure to the pulmonary artery may gradually produce arteriolar thickening in the pulmonary vascular bed, with the development of pulmonary hypertension In fact, the pulmonary arterial pressure may eventually approach the systemic pressure, due both to the shunt and to increased pulmonary arteriolar resistance, and at this point the surgical mortality becomes prohibitively high The level of from 70 to 80 mm Hg systolic for pulmonary arterial pressure is frequently considered an arbitrary dividing line between patients who should do well following closure of the ductus and those who will not Of course, the lower the pulmonary arterial pressure the better, and the higher it is the more unfavorable the prognosis In some patients the pressure in the pulmonary artery may exceed that in the aorta, and blood then passes in the reverse direction, perhaps producing cyanosis of the lower half of the body This is a sinister omen, and right heart failure may soon follow

In addition to the deleterious effects of pulmonary hypertension on the right ventricle, the A-V fistula increases the work of the left ventricle Finally, bacterial infection may be engrafted upon the fistula, and progressive calcification and shortening of the ductus may render it difficult or hazardous to close in adult life

There may be a *thrill* over the precordium The ECG is usually normal, and the presence of significant right axis deviation should at least suggest the possibility of some other lesion, such as isolated pulmonic stenosis or tetralogy of Fallot Roentgenologic changes, other than visualization of the fistula on angiography, are not particularly specific in the presence of a patent ductus There is often some prominence of the pulmonary artery, and under fluoroscopy the so-called "hilar dance" may be observed, due to the rapid flow of blood into the pulmonary artery from the aorta during systole In children cardiac enlargement is usually not marked and right ventricular enlargement has usually not developed, as it may over the years from a prolonged increase of pressure in the pulmonary artery In general, the greater the diameter of the patent ductus arteriosus, the more marked will be the roentgen changes

Surgical management of patent ductus Since Gross first successfully ligated a patent ductus arteriosus in 1938, literally thousands of these operations have been performed The ductus may be ligated with multiple ligatures or it may be divided Because recurrence rates as high as 10 per cent have been reported following ligation, our present policy is to place clamps across the fully exposed ductus, partially dividing and partially suturing both the aortic and the pulmonary ends in stages (Fig 152) In

this way the ends are almost closed before the ductus has been completely divided, reducing the chance of hemorrhage should the clamps slip, and by division of the ductus the possibility of late recanalization is virtually eliminated. Rarely for technical reasons, multiple ligations may be preferable to division. As an added safety measure the aorta should be mobilized both above and below the ductus In older subjects where aortic hemorrhage is a genuine possibility it is particularly important to have mobilized the aorta sufficiently to permit cross-clamping if necessary

Operative results If operation is performed in children before marked pulmonary hypertension heart failure calcification, or subacute bacterial endocarditis has occurred the mortality should be less than 4 per cent. After age 20 the older the patient the greater the risk Without operation life expectancy is probably in the general neighborhood of about 40 to 50 years of age the chief cause of death being heart failure or the development of subacute bacterial endocarditis (from the stress of the fistula?) Whereas these are the two chief complications the general retardation of physical development in childhood should be mentioned and occasionally aneurysmal dilatation of the ductus may result in rupture with death from this cause In an analysis made by Keys and Shapiro,[92] it was found that subjects who are alive at the age of 17 years have a subsequent life expectancy which averages only approximately one-half that of the general population Gross believes that the ductus should be closed up to middle age after which the increased difficulty of the operation (because of the depth of exposure and the increased rigidity of the involved vessels) renders the procedure hazardous and thus possibly not indicated unless definite symptoms of heart failure develop Furthermore the size of the communication in such subjects is obviously a small one for the presence of a large arteriovenous fistula would have caused heart failure and other complications

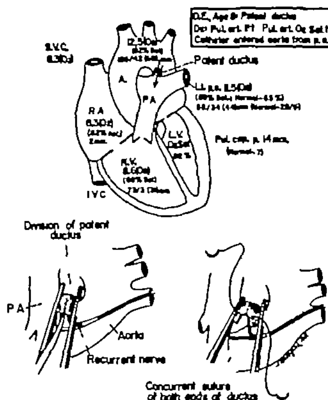


Fig 153 The patent ductus arteriosus illustrates the more important diagnostic criteria to be obtained by cardiac catheterization in any heart condition (1) abnormal pressures, (2) abnormal oxygen saturation, and (3) the passage of the catheter through abnormal openings. It is not necessary to catheterize the typical case of patent ductus arteriosus to make the diagnosis. The murmur may be virtually diagnostic (Catheterization data supplied by Dr Thomas M Blake)

at an earlier age Following operation the diastolic blood pressure rises, as it does following the closure of other arteriovenous fistulas and the murmur and the thrill disappear Occasionally however, the systolic murmur persists due to dilatation of the pulmonary artery Measurements of heart action show that the cardiac effort is diminished following closure of the fistula.

AORTIC PULMONARY SEPTAL DEFECT A congenital communication between the first parts of the ascending aorta and the pulmonary artery just above the semilunar valves is an uncommon lesion. Nevertheless it is well to be aware of this possibility when operating for patent ductus since the aortic pulmonary septal defect so closely mimics the patent ductus that it is usually encountered unexpectedly Yet, to close this fistula is far more difficult technically than

to close the patent ductus This is because the aortic-pulmonic septal defect is closer to the heart, is of greater length, and represents a side-to-side anastomosis rather than two separate arteries joined by a vessel of some length While the first successful closure by Gross[67] was accomplished by ligating the communication and subsequent ones by cross-clamping using special clamps (with division and suture), Cooley and his associates[38] have emphasized the hazards of such an approach They suggest that the surgeon be prepared to employ either hypothermia or the pump oxygenator, should a septal defect be found instead of the anticipated patent ductus arteriosus Otherwise, severe hemorrhage from the undersurface of the communication may prove uncontrollable

COARCTATION OF THE AORTA *Pathology* Coarctation of the aorta is a constriction which most often occurs adjacent to the aortic termination of the ligamentum arteriosum, just distal to the origin of the left subclavian artery (Fig 153) The constriction may also occur either proximal or distal to this point In fact, coarctation may occur almost anywhere in the thoracic aorta Many prefer to attempt to classify the cases into the so-called "infantile" and "adult" types, but I have found little practical aid in such a classification Rather, I would prefer to utilize the following more precise descriptive classification of Edwards [50]

A Coarctation of the aorta with closed ductus arteriosus
  1 Coarctation in the vicinity of the ligamentum arteriosum
  2 Coarctation in unusual locations
  3 Coarctation with stenosis of the right or the left subclavian artery
B Coarctation of the aorta with patent ductus arteriosus (about 10% of cases)
  1 Coarctation distal to the aortic mouth of the ductus
  2 Coarctation proximal to the aortic mouth of the ductus

The so-called "adult type" of coarct[...] may be found in infants, and the "infa[...] type," supposed to be characterized [...] more elongated constriction, may be f[...] in adults Thus, we see little practical u[...] for these terms at the present time, par[...] larly since homografts may be inserte[...] bridge the defect if the ends of the div[...] aorta cannot be brought together wit[...] undue tension Incidentally, even thoug[...] operation for coarctation the ductus [...] not appear to be patent it should be lig[...] for this precaution may avoid trouble[...] hemorrhage at the time of operation [...] perhaps disastrous hemorrhage postop[...] tively If a patent ductus is situated d[...] to the coractation, increased pressure in [...] pulmonary artery (and the lowered a[...] pressure below the constriction) may [...] duce flow through the ductus to the d[...] aorta However, if the development of [...] lateral circulation around the coarcta[...] has been extensive, the pressure in the di[...] aorta will be sufficient to cause blood to [...] through the ductus from the aorta to [...] pulmonary artery, in the usual man[...] Should the flow from the pulmonary ar[...] to the distal aorta be sufficiently la[...] there would be some degree of cyanosis [...] the lower portion of the body

The lumen of the coarcted segm[...] varies considerably in size, but it is usu[...] markedly stenosed and at times is abs[...]

Etiology of hypertension in coarctati[...] In a particularly appealing series of stud[...] Scott and Bahnson[131] investigated the r[...] of the kidney in the development and ma[...] tenance of hypertension in experimen[...] coarctation of the aorta Using dogs, th[...] produced coarctation and noted a gradua[...] progressive rise in carotid pressure wh[...] reached a hypertensive plateau in from [...] to 7 weeks after the production of [...] coarctation There was an immediate f[...] in femoral arterial pressure after operatio[...] followed by a slow rise to normal and, [...] some instances, to supranormal levels Su[...] sequently, transplantation of a kidney [...] a level above the coarctation, with contr[...]

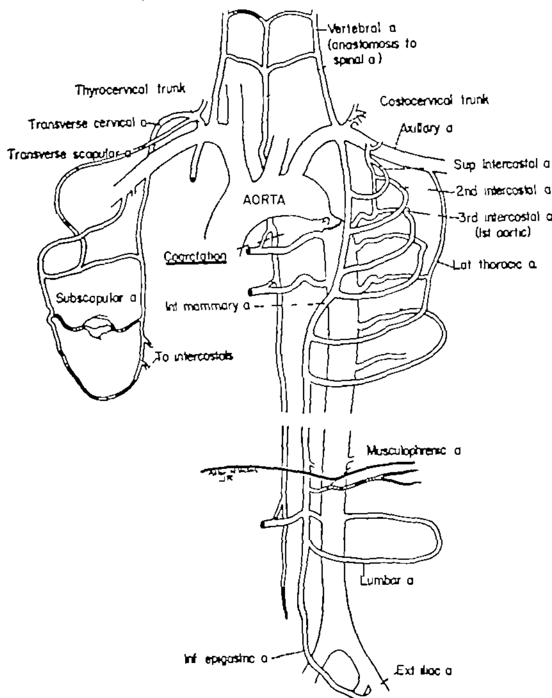


Fig 153 The cause of proximal hypertension in coarctation of the aorta is not entirely settled, but both mechanical and renal factors have been implicated.

lateral nephrectomy resulted in disappearance of hypertension in 5 animals with experimental coarctation No change in hypertension occurred in another animal with coarctation when a kidney was transplanted to the groin and contralateral nephrectomy performed. It was concluded by Scott and Bahnson that hypertension in experimental coarctation is mediated through a renal mechanism, and subsequent studies have strengthened this view

In discussing the etiology of hypertension in the presence of coarctation, Little[106] noted that if the cause were mechanical then variations in the degree of the stenosis of the aorta and in the extent of the collateral circulation developed would be expected to cause wide fluctuations in the

degree of hypertension in individual cases Moreover, aside from mechanical considerations, variations in blood flow to the kidneys might also be expected to influence the degree of hypertension if the renal contribution to the hypertension were important

Diagnosis The symptoms of this condition are few, though an occasional patient may complain of fatigue or coldness in the feet and legs In a young person, hypertension in the arms with absent or weak foot pulses should always suggest the presence of coarctation of the aorta The comparison of the pressure in the arms with that in the legs is important, for the blood pressure in the legs is normally higher than that in the arms Additional diagnostic aids consist of the plain roentgenogram which may show hypertrophy of the left ventricle, notching of the ribs, and a deformity of the normal outline of the descending aorta at the arch

Angiography can be used to demonstrate the coarctation. Successful visualization of the defect is occasionally achieved by injection of the radiopaque medium into an antecubital vein, but retrograde injection through the left common carotid artery is much more effective in demonstrating the defect However, mishaps have plagued retrograde injection and we have abandoned it, feeling that the routine use of this method will result in greater morbidity and mortality than will the rare unnecessary thoracotomy where the diagnosis is in error For example, I have personal knowledge of 3 fatalities which occurred following retrograde angiography through the left carotid for visualization of the coarctation An alternative method is to pass a cardiac catheter through a femoral artery and up the aorta [163]

Prognosis without operation Although patients may live through a completely normal life span with coarctation of the aorta, the general life expectancy without surgical treatment is on the order of between 35 and 40 years In contrast, life expectancy is presumably rendered nc if the operation is performed early en When death occurs it is usually due complication of the hypertension, to ca failure, or to aneurysm formation and ture of the aorta proximal to the poi coarctation

Surgical correction of coarctation o aorta Coarctation of the aorta was successfully resected with end-to-end a tomosis by Crafoord of Stockholm in followed a very short time later by a ilarly successful operation by Gross operation is now commonplace and is formed in most hospitals in which surgery is done Whereas there was merly considerable concern preoperati on the part of the surgeon as to wheth not the length of the constriction migh such that the ends of the aorta could nc brought together without undue tension lowing resection, this has not been so s Gross[60] reported in 1951 that the us arterial homografts produced satisfac results

In contrast to the brief time that normal thoracic aorta can be occluded operation without risking spinal cord d age, the surgeon may take the necess time to perform a meticulous anastom following resection of a coarcted segm since virtually no blood has been flow through this segment previously Yet, more intercostal arteries than necess should be divided, since many collate (Fig 153) have already been divided performing the thoracotomy and an exc sive reduction of collateral circulation m result in spinal cord damage In fact, t complication has been reported in the erature Every effort should be made avoid occluding the left subclavian art during the resection, and this may often accomplished by placing a clamp obliqu (tangentially) across one side of the u ally large left subclavian artery to pen relatively normal blood flow to contin through this vessel, even when the po of coarctation is immediately distal to

point of origin from the aorta. Or, the Potts exclusion clamp may be used. Paralysis and death have been reported in a patient whose left subclavian artery was also cross clamped at the time of resection of the coarctation.

Aortic growth following resection in children. Considerable discussion has centered around the proper method of suture of the aorta following excision of the coarctation, since presumably in children the aorta must subsequently either grow to adult size or render the recurrence of coarctation probable. Johnson and Kirby[90] studied this question in pigs and found that it was probably desirable, in children, to use interrupted sutures on at least a portion of the circumference of the aorta. In patients who have reached the age of 15 or more, however, a simple continuous suture or an everting continuous mattress suture of 5-0 or 4-0 arterial silk is usually satisfactory.

Postoperative course. Every effort must be made to avoid infection, which all too often will result in a rupture of the anastomosis. It is obviously important, particularly in patients whose defect tapers gradually down to the point of maximal constriction, to excise a sufficient length of the aorta on either side of the constriction to permit the establishment of a lumen of normal size; else the hypertension will not subside postoperatively. The presence of a thrill in the aorta at the point of anastomosis following release of the clamps indicates that the lumen is constricted and, usually, that additional aorta should be resected.

If in the immediate postoperative period the blood pressure in the legs is higher than that in the arms and if the patient has good bounding pulses in his feet, it may be anticipated that the brachial arterial blood pressure will fall to normal levels over the course of the next 2 or 3 weeks, if it does not do so immediately (Fig. 154).

Paradoxical hypertension. Most surgeons have observed patients who, following resection of a coarctation, exhibited for several days continued hypertension equal to or greater than that recorded preoperatively—at times associated with pallor, abdominal pain, sweating, apprehension, palpitation, tachycardia, and some fever. Sealy and co-workers[134] found this response to be due apparently to an increased secretion of norepinephrine. They reported a case of gangrene of the bowel which had resulted from the vasospasm they believed was produced by the sympathomimetic hormones.

TETRALOGY OF FALLOT. "Ask a group of medical students today about the pathology of the tetralogy of Fallot and almost in unison they will say: Stenosis of the pulmonary artery, interventricular septal defect, dextraposition of the aorta and hypertrophy of the right ventricle. The same question put to a group of cardiologists ten years ago would have called forth hesitant mumblings from a few who had taken mild academic interest in the subject. Nothing stimulates greater interest in a disease, hitherto completely hopeless, than the discovery of an effective therapeutic procedure. To Blalock and Taussig goes all the credit for the tremendous interest which their operation aroused in the congenital heart deformity known as tetralogy of Fallot."[123]

Pathophysiology. Tetralogy of Fallot is the most common of the congenital cyanotic lesions of the heart (Fig. 155). There is a right to left shunt which results in the passage of desaturated blood from the right ventricle into the aorta and the systemic circulation. The shunt occurs because of the fact that there is a defect high in the membranous portion of the interventricular septum and because the aorta tends in varying degrees to overlie the septum, receiving blood from each ventricle. In addition, stenosis of the pulmonary artery results in increased resistance, and so in systole further unsaturated blood is forced into the aorta from the right ventricle. Since a limited amount of blood can enter the pulmonary artery, pres-

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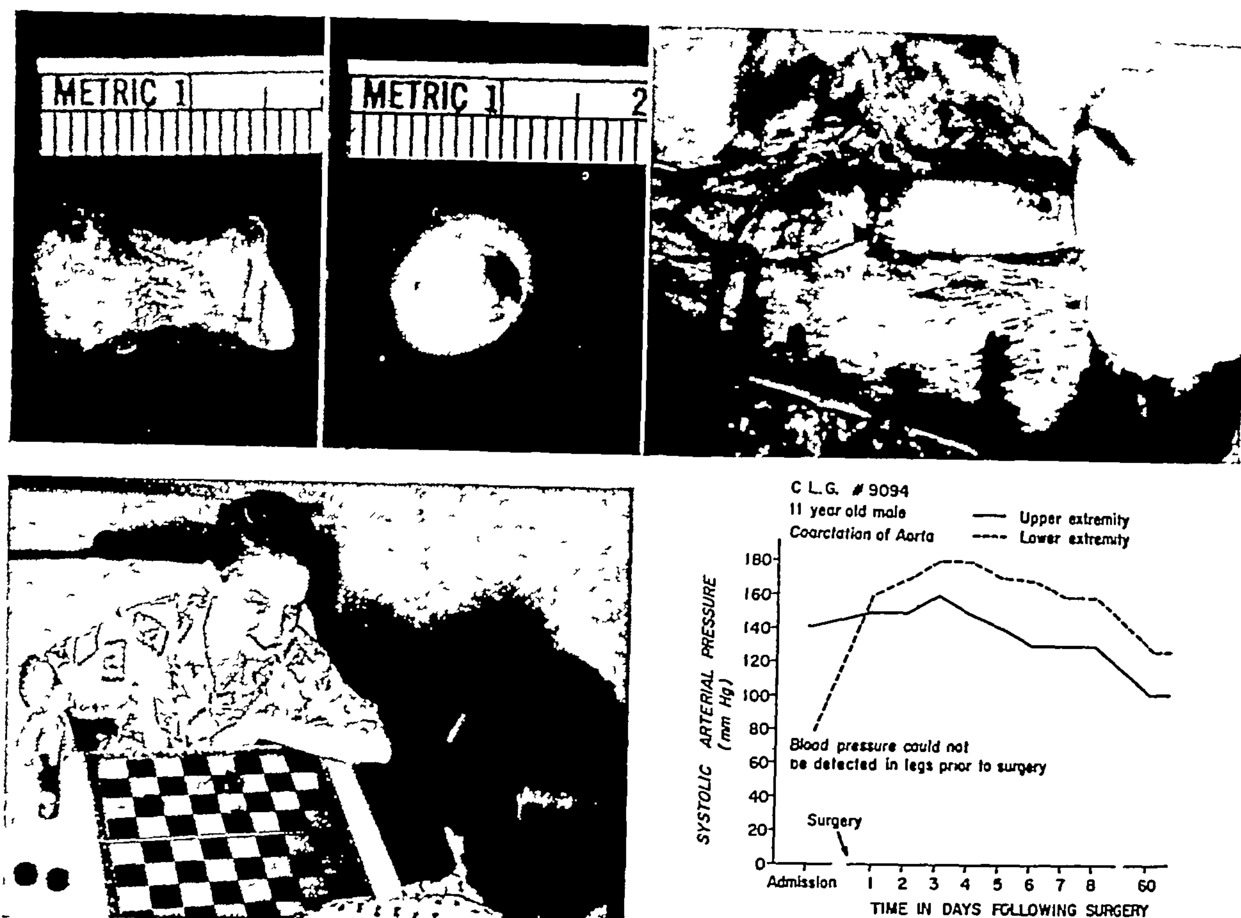


Fig 154 Case study C G, 11 years old, had all his life had cold feet, and when he exercised he found that his legs got tired easily During a routine check-up he was found by his family physician to have hypertension, and the diagnosis of coarctation of the aorta was made The parents postponed surgery for many months, until an episode of probable hypertensive encephalopathy with brief coma prompted immediate action *Upper left* The excised coarcted aortic segment with very small (0 4-cm) lumen *Upper right* Aorta following end-to-end anastomosis *Lower left* Patient 5 days following surgery *Lower right* Blood pressures in arms and legs before and following surgery Note that before operation the pressure in the legs was not obtainable but that thereafter the pressure in the legs exceeded that (now normal) in the arms

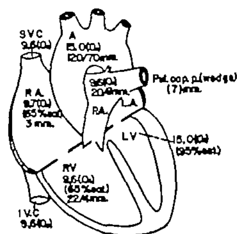
sure in the right ventricle is elevated but that in the pulmonary artery is reduced

The *cyanosis* is usually present from the time of birth, though occasionally it may not develop for several months, due to the fact that the ductus arteriosus remains open for that length of time The cyanosis may be severe and may become progressively worse, or it may be quite mild while the child is at rest The right ventricular hypertrophy is presumably due partly to the increased pressure imparted by the left to right shunt through the interventricular septal defect, this increases the pressure against which it must pump, in addition to the aforementioned increased resistance in the pulmonary outflow tract resulting from stenosis either in the infundibulum or the pulmonary artery itself

Clinical findings The *arterial oxygen desaturation* (60 to 90 per cent) which results in cyanosis also produces dyspnea A characteristic observation is that the child squats when he is dyspneic and that squatting appears somewhat to relieve the dyspnea In fact, this finding is of considerable diagnostic aid It has been shown that this position apparently increases the venous return to the right heart, and that diminished cardiac output may account to a considerable degree for the dyspnea and its relief by squatting which increases cardiac output

Clubbing of the fingers and toes is usu-

PATHOPHYSIOLOGY OF TETRALOGY OF FALLOT



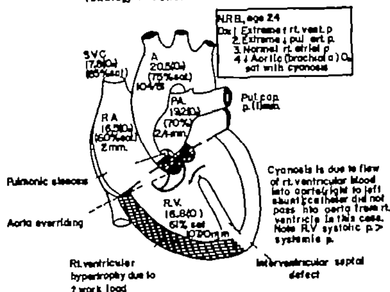


Fig 155 The markedly elevated pressure in the right ventricle has produced right ventricular hypertrophy The pulmonary artery pressure was very low Overriding of the aorta with interventricular septal defect produced cyanosis. (Catheterization data supplied by Dr Thomas M Blake)

ally observed in association with cyanosis, as is *polycythemia*, the red cell count ranging from 6 to 7 million per cu. mm. of blood. The cardiac *murmur* most commonly present is a systolic murmur to the left of the sternum which varies considerably in character and intensity *Roentgenograms* characteristically show a "boot-shaped heart with a blunted apex and a concavity in the region of the pulmonary segment. *On fluoroscopy* there is a paucity of vascular markings in the lung fields, and the hilar pulsations of the normal pulmonary artery are diminished or absent. The ECG characteristically shows evidence of right axis deviation due to right ventricular hypertrophy, and the absence of right ventricular hypertrophy militates considerably against the presence of tetralogy of Fallot.

While the typical case may be diagnosed with reasonable certainty on the basis of the findings already mentioned the cyanotic patients with atypical findings will require the most careful study and interpretation and in these, angiography and particularly cardiac catheterization will be most helpful

By *angiography* the septal defect may be revealed through premature filling of the aorta from the right ventricle, due to the fact that the aorta overrides the ventricular septum (at least physiologically) Late filling of the lung vasculature is a result of the obstruction to the entrance of blood from the right ventricle into the pulmonary artery

Cardiac catheterization may demonstrate that the catheter can pass from the right ventricle into either the aorta or the pulmonary artery and, of course, it may pass into the left ventricle because of the septal defect. The systolic pressure in the right ventricle may approach that in the aorta (i.e, brachial arterial pressure), whereas the pressure in the pulmonary artery is low (Fig. 155) Since the pressure relationships which usually exist favor the shunt of unsaturated blood from the right ventricle to the left ventricle and into the aorta the oxygenation of the blood in the right ventricle is not increased above usual veno

values, as it would be if the shunt were from left to right Kjellberg and his associates[95] prefer to do cardiac catheterization on most cases and to perform angiocardiography through the cardiac catheter Our own policy is that virtually all cyanotic children be catheterized, to provide all possible information relative to the location and physiologic characteristics of the defect

Correction of tetralogy of Fallot The one of the four defects of the tetralogy which originally permitted surgical amelioration of the condition was pulmonic stenosis In 1945 Blalock and Taussig[28] conceived the idea of passing additional blood through the lungs to permit increased oxygenation They achieved this by anastomosing a subclavian artery to a pulmonary artery, creating an "artificial patent ductus arteriosus" Whereas prior to operation the arterial oxygen saturation might have been on the order of 70 per cent, the value was increased to perhaps 80 to 90 per cent following their procedure When the length and especially the diameter of the subclavian artery proved difficult to work with in some of the very young, Potts, Smith, and Gibson[123] reported a method of anastomosing the aorta directly to a pulmonary artery by means of a special clamp which permitted continued flow of blood through the aorta while pinching off a portion of its wall adjacent to the pulmonary artery, permitting construction of a side-to-side fistula By this means an opening of a definite size was produced, usually approximately 6 mm , and this operation has been widely adopted for use in infants

These artificial shunts produced dramatic improvement in patients with tetralogy of Fallot, albeit by virtue of having produced still another defect, and they stimulated prodigious enthusiasm and investigation in the field of congenital heart disease Subsequently it was suggested that, instead of producing a fifth defect, the defects be reduced to three by passing a rongeur through a purse-string suture in the wall of the right ventricle and excising the stenosing tissue in the infundibulum : base of the ventricle However, this resented a blind and more difficult cedure and the mortality was, in hands, higher than that which was ciated with the more simple shunt dures Later, Lillihei and his associa at Minnesota excised the stenosing under direct vision and also closed tl terventricular septal defect in patients tetralogy of Fallot, using first the circulation technic and later the p oxygenator At this writing their mor has ranged from 20 to 30 per cent, wh the mortality associated with the Bla Taussig and Potts-Smith-Gibson p dures has ranged from 10 to 15 per Nevertheless, it is probable that in future complete correction of the tetr of Fallot will be carried out under vision in a bloodless field at the tin open heart surgery Meanwhile, the ficial shunts provide much benefit and be performed by competent surgeons al anywhere—until the problems atten upon the use of the pump-oxygenator been sufficiently solved to permit safe eral use of dependable equipment operation of patients who need it ca performed at a later age

Prognosis following a shunt operatio tetralogy of Fallot[151] Although the life span of these patients cannot ye determined, as little more than 10 y has passed since the first patients operated upon, approximately three-fou of those coming to surgery have been siderably benefited Improvement con of increased exercise tolerance, diminis cyanosis and clubbing, and reduced p cythemia In most of the successful c a continuous murmur can be heard at site of the anastomosis, in fact, the p ence of this murmur soon after opera is a favorable prognostic sign The an mortality rate has not been much abov per cent, and this has included the ri to which these patients are inevitably posed whether they have an operation

not Heart size has not increased as much as the presence of a fistula would have been thought likely to occasion. For example, Campbell and Deuchar[36] found that the cardio-thoracic ratio might increase quickly from 48 to 52 per cent but then remain constant during the period of observation.

CONGENITAL (PURE, ISOLATED) PULMONIC STENOSIS. *Definition and pathophysiology* The term congenital pulmonic stenosis is used to denote one or more types of obstruction in the pulmonary outflow tract.[94] The obstruction may be located (1) in the pulmonary artery itself (pulmonary atresia), (2) at pulmonary valve (valvular stenosis), and (3) in the outflow portion of the right ventricle (infundibular stenosis) Tricuspid atresia may also simulate pulmonic stenosis. Obviously the anatomic nature of the obstruction will have much to do with methods of approach to it and with the success that can be achieved.

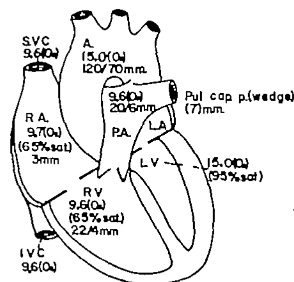
Pulmonic stenosis will here be considered as occurring in the absence of a septal defect and furthermore, particular attention will be devoted to those cases in which the chief pathology consists of a conelike fusion of the cusps of the pulmonary valve, which fusion may vary from a negligible degree to almost complete (pinpoint) occlusion.

The pulmonary artery is usually dilated beyond the point of stenosis, the characteristic so-called "post-stenotic dilatation (Figs. 156 and 170) Moreover, in general the more severe the stenosis the greater the degree of post-stenotic dilation The largest pulmonary artery that I ever saw was encountered in a 35-year-old woman with this disease who was operated upon. Successful pulmonic valvulotomy was per-

PATHOPHYSIOLOGY OF ISOLATED PULMONIC STENOSIS

Pressures and blood oxygen saturations in a normal heart

SC age 5
Pure pulmonic stenosis
O_2 saturations normal
pressures diagnostic



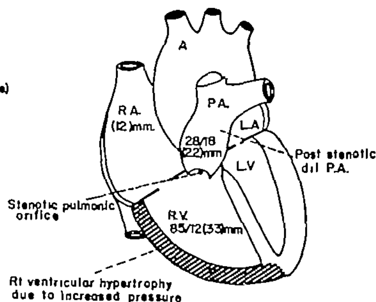


Fig 160 The diagnosis of pulmonic stenosis is established by demonstrating a gradient of diminishing pressure between the right ventricle and the pulmonary artery In this patient a normal or slightly elevated pulmonary artery pressure (28/18) was achieved at the expense of a marked rise in right ventricular pressure. The measurement of only pulmonary artery pressure in this subject would not have indicated the pulmonic stenosis. (Catheterization data supplied by Dr Thomas M Blake.)

formed through the wall of the right ventricle near the pulmonary outflow tract Improvement was such that, whereas previously she was almost continually in cardiac decompensation, she was subsequently able to perform her active housework and to resume her position as a secretary with an insurance company

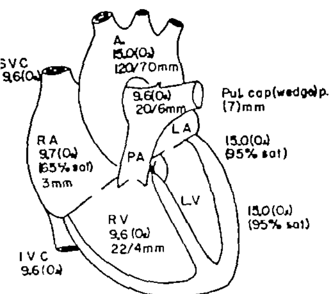
A patent (or potentially patent) foramen ovale is often associated with pulmonic stenosis, and if this defect is sufficiently large and the pressure in the right atrium sufficiently elevated, a right-to-left atrial shunt may result in cyanosis However, in the absence of such interatrial or interventricular septal defects, which are not under discussion at this point, these patients are not cyanotic unless actual heart failure with the cyanosis so produced has supervened In other words, while pulmonary outflow obstruction diminishes cardiac output, all blood that is ejected into the systemic arteries has passed through the lungs and is saturated Yet, the dyspnea and decreased exercise tolerance may be marked Cardiac enlargement is usually associated with a systolic murmur at the base of the heart and perhaps a thrill Right ventricular enlargement is present but the lung fields are clear, since too little rather than too much blood flows through the pulmonary bed The increased effort of the right ventricle results in right axis deviation in the ECG, evidence of right ventricular strain *Cardiac catheterization* reveals considerably increased pressure in the right ventricle with a relatively low pressure in the pulmonary artery beyond the point of stenosis By noting changes in pressure along the pulmonary outflow tract, it may be possible to localize the site of stenosis as being in the infundibulum or at the pulmonic valve or both Moreover, pressure measurements at operation may reveal a second point of stenosis after relief of a first. Oxygen values are normal. *Angiography* exhibits no overriding of the aorta or septal defect, but the medium remains abnormally long in the right ventricle, slow filling of the lung fields

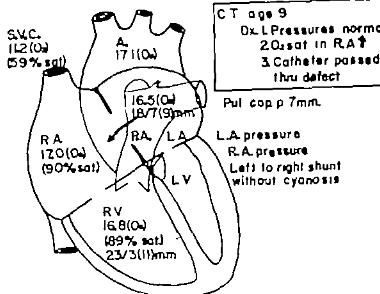
Surgical correction consists of intro ing a valvulotome through the wall of right ventricle, advancing it into the monary outflow tract,[31] and thus enlar the opening in the pulmonary artery an alternative approach, the stenosis be relieved under direct vision, using e hypothermia or the pump-oxygenator operation, the location of the thrill in pulmonary outflow tract is perhaps the si most reliable indicator of the site of struction Palpation of a domelike, stiff monic valve further localizes the sten at this point

Results are generally good, particul when the stenosis affects the cusps of pulmonic valve itself, and the operat mortality is low Postoperative catheteri tion should reveal a substantial reduct in right ventricular pressure and an ele tion in pulmonic arterial pressure

ATRIAL SEPTAL DEFECT (FIG 157) A pat foramen ovale is present in from 20 to per cent of all adults, but in most ca the septa are fully developed and the va covers the opening, though it is imp fectly fused Yet, in some patients an acti left-to-right shunt exists If the opening small, the individual may live a norm life span without symptoms If it is lar the shunt may markedly increase (4 to times) the flow of blood (recirculatio through the right side of the heart and t pulmonary circuit, leading to right-sid heart failure in early or middle age Sin normally the pressure in the left atrium higher than that in the right, these patien are usually not cyanotic On the other han should pulmonary pathology develop to t extent that the pressures in the pulmona artery, right ventricle, and right atriu are sufficiently increased, the septal def (or the patent foramen ovale that was pr viously functionally closed) may permit right to left shunt to develop, producin cyanosis

PATHOPHYSIOLOGY OF ATRIAL SEPTAL DEFECT





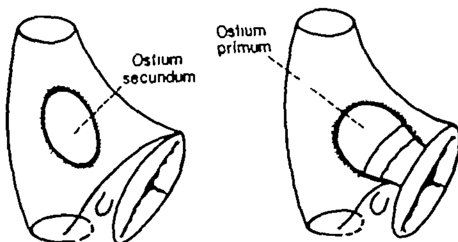


Fig 157 The recirculation through the lungs of oxygenated blood passing from the left atrium to the right atrium increases the work load of the right ventricle The increase in flow through the pulmonary vascular bed may thus be great. Right heart failure eventually ensues, but an interatrial septal defect of even moderate size is often well tolerated for many years. (Catheterization data supplied by Dr Thomas M. Blake.)

Diagnosis The development of surgical technics for the closure of atrial septal defects spotlighted the need for more precise diagnostic information including the size and location of the defect and the exclusion or identification of other heart lesions. While the clinical diagnosis of an uncomplicated atrial defect is usually made without difficulty on the basis of clinical data and roentgen examination, *cardiac catheterization* is necessary to verify the diagnosis to estimate the amount of shunted

(recirculated) blood, and to measure the pressure in the pulmonary artery The passage of the catheter from the right atrium to the left atrium does not necessarily establish that a shunt exists, since the catheter may have passed through a small probe-patent foramen ovale, nevertheless, if the arterial oxygen saturation in the right atrium is higher than that in the cavae, a left to right shunt is present In the usual case, pressure measurements are not too helpful, since the pressure gradient from left to right need not be large

It may be difficult to differentiate an atrial septal defect from a high ventricular septal defect, or from multiple other defects such as anomalous drainage of pulmonary venous flow into the right atrium However, using all available evidence, plus angiocardiography, the diagnosis can usually be made In a pure atrial septal defect the angiocardiogram is not very helpful, since the direction of interatrial flow is from left to right

Finally, it is important, when possible, to differentiate the ostium secundum defect from the far more complicated ostium primum and common atrioventricular canal At thoracotomy the nature of the defect can be further defined by first exploring with the finger through the atrial appendage, prior to formal cardiotomy

The *murmur* of atrial septal defect is moderate in intensity and is heard best over the second left interspace On *roentgenogram* the right heart is not enlarged unless the shunt is of moderate size The ECG is likely to show incomplete right bundle branch block, combined with right ventricular hypertrophy and thus right axis deviation

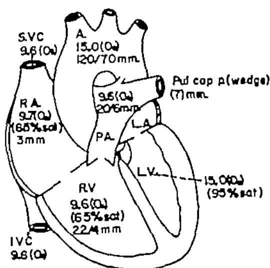
Surgical treatment The ostium secundum defects have been closed by a variety of methods Bailey[6] and others inverted the atrial appendage to close the defect Gross[70] advanced the atrial well technic, while Swan[148] and Lewis[101] employed hypothermia Bjork and his associates[25, 26] advocated the circumferential suture technic However, the more serious ostium primum complex is not readily amenable to correction with these methods, and open heart surgery using the pump-oxygenator is probably the method of choice

INTERVENTRICULAR SEPTAL DEFECT (FIGS 158 AND 159) *Pathophysiology* Interventricular septal defect is one of the members of the tetralogy of Fallot, but it may also occur separately The isolated defect is usually high in the membranous portion of the septum, and may vary in size from a very small opening to one several centimeters in diameter Much more rarely, a defect may be present in the muscular portion of the septum—congenital, traumatic, or secondary to infarction The severity of the circulatory derangement and attendant symptomatology are proportional to the size of the opening Small defects allow only a slight shunt of blood from the left ventricle into the right ventricle and pulmonary artery Large defects allow much blood to pass through the opening from the left ventricle to the right ventricle, because of the marked pressure difference The increased pressure and flow in the right heart and pulmonary circuit leads to right ventricular enlargement and pulmonary hypertension due to changes in the pulmonary vascular bed The pressure in the right ventricle may eventually exceed that in the left ventricle, at which time the shunt changes from left to right, to right to left, and cyanosis appears Right heart failure follows

Diagnosis Symptoms may be absent or minimal if the defect is not large In fact, a small defect which produces a murmur but little else is compatible with a long life Thus, the murmur *per se*, which is characteristically harsh and heard best in the third or fourth interspace to the left of the sternum, is not an indication for surgery A thrill may be present

Roentgenograms may reveal hypertrophy of the left ventricle, due to the increased work load imposed by the shunt, and hyper-

PATHOPHYSIOLOGY OF INTERVENTRICULAR SEPTAL DEFECT



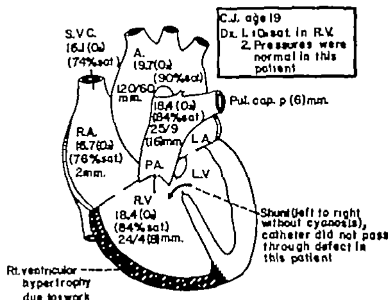
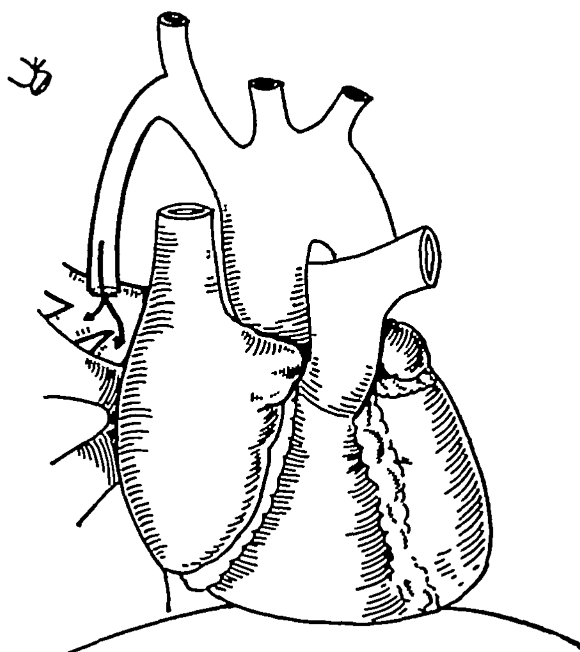


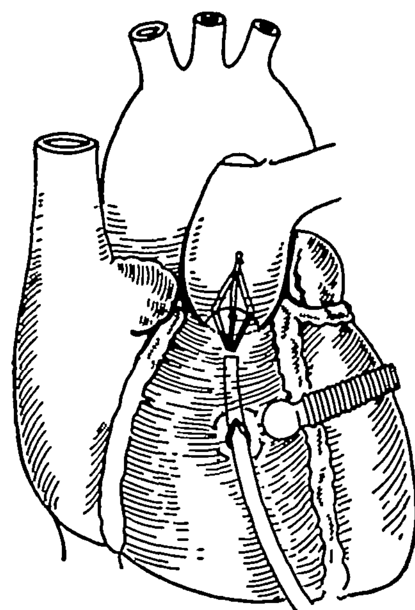
Fig 168 Interventricular septal defects are diagnosed by physical examination and by cardiac catheterization. Angiocardiograms are less informative because the shunt is from left to right that is, the contrast medium flowing into the right ventricle from the right atrium might be diluted by the shunt, but the left ventricle would not be visualized prior to visualization of the lung fields the aorta would not be filled prematurely unless there was overriding—which condition would no longer represent a simple interventricular septal defect. The left ventricle may also exhibit hypertrophy (Catheterization data supplied by Dr Thomas M Blake)

trophy also of the right ventricle. Pulmonary hypertension may develop The ECG may show evidence of left ventricular hypertrophy if pulmonary hypertension is not present however, hypertrophy of both ventricles may be noted. Angiocardiography is not particularly helpful. *Cardiac catheterization* is especially valuable if the catheter can be made to enter the aorta from the right ventricle. Not as definitive, but valuable is demonstration of increased oxygen saturation in the right ventricle as compared with the right atrium. Measurements of blood flow may reveal a pulmonary flow that is many times the systemic flow, if the defect is large and pulmonary resistance low If the catheter enters the defect promptly it may be difficult to determine whether or not overriding of the aorta is present or a simple interventricular defect is present. In this event, angiography may disclose a normal aortic root. If the patient has a sizable *right to left* shunt because of severe right ventricular (and pulmonary) hypertension it may be possible to distinguish an atrial septal defect from a ventricular septal defect by injecting Evans blue dye through the catheter If the circulation time to a recording oximeter on the ear is less when the dye is ejected in the right ventricle than in the pulmonary artery, then a ventricular defect is present. A small ventricular septal defect is not easy to diagnose unless the catheter can be passed through it.

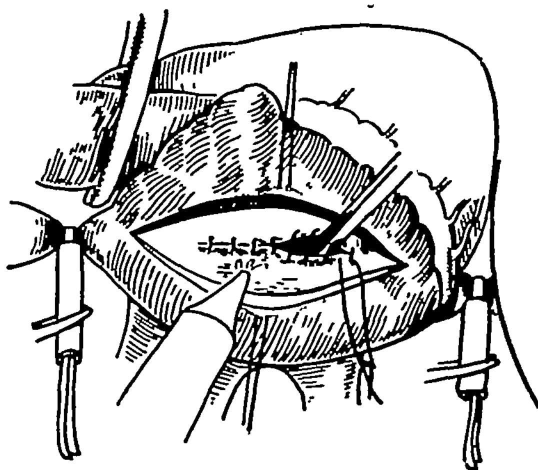
Surgical correction of interventricular septal defect A considerable number of interventricular septal defects have now been



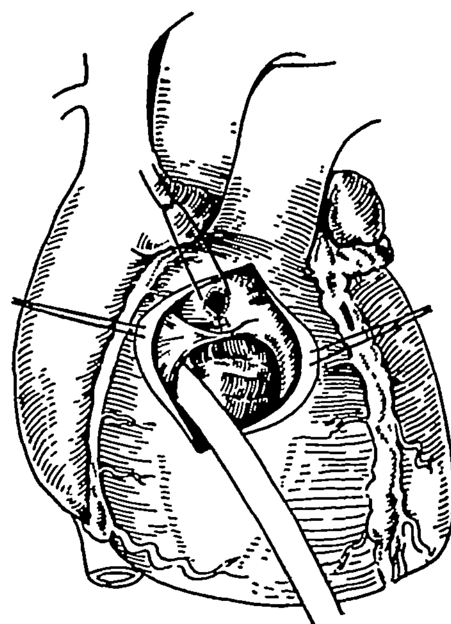
Blalock anastomosis



Brock valvulotomy



Closure of an atrial septal defect under direct vision using hypothermia



Simple suture

Fig 159 Representative corrective operations for tetralogy of Fallot, isolated pulmonic stenosis, interatrial septal defect and interventricular septal defect Open heart surgery is permitting rapid modification of previous concepts and technics

closed successfully, in some cases under hypothermia but far more often using a pump-oxygenator (Fig 160) However, the operative mortality has ranged in the neighborhood of 30 per cent, and unless the defect is large and producing significant symptoms and pulmonary hypertension, it would appear advisable to temporize until further experience with the pump-oxygenator[32] has accumulated On the other hand, where the size of the defect is producing physi[illegible] derangements which justify the oper[illegible] risk, surgery should be performed Th[illegible] some evidence that pulmonary hyperte[illegible] present in infancy does not invariably [illegible]sist in later years [42]

TRANSPOSITION OF THE PULMONARY V[illegible] Various degrees of pulmonary venous d[illegible]age into the right side of the heart ma[illegible] cur, and occasionally the entire venous

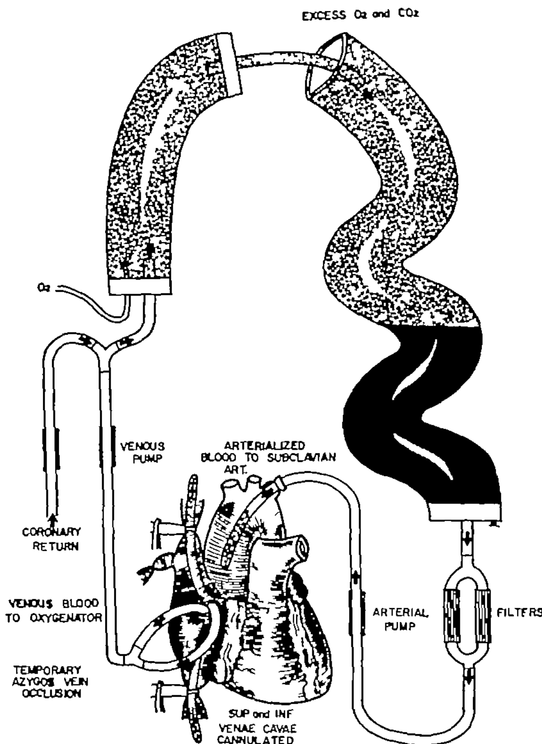


Fig 160 The DeWall Lillehei pump-oxygenator The blood is removed from the venae cavae at the left and pumped into the helix. Oxygen is bubbled through the blood as it rises upward and flows across to the right. As it flows downward the now oxygenated blood releases CO_2 to the air The blood then passes through the filters, and an arterial pump returns the oxygenated blood to the left subclavian (or femoral) artery A number of different oxygenators are now commercially available but basically all are designed for extracorporeal oxygenation of the blood and the removal of CO_2

monary drainage may enter the right heart. Whereas partial drainage of the pulmonary veins into the right side of the heart is readily compatible with life total anomalous drainage is not well tolerated, death *usually occurring before the age of 6* months. For life to continue in the presence of complete pulmonary drainage into the right atrium, there must exist some connection between the right and left sides of the

heart, usually a patent foramen ovale or an interventricular septal defect Muller[116] reported 2 cases, 1 successful, in which the venous drainage from the left lung was anastomosed to the left atrial appendage Cyanosis diminished Further success in the correction of this condition has already been achieved at open heart surgery using the pump-oxygenator

TRANSPOSITION OF THE AORTA AND PULMONARY ARTERY Thus far the treatment of this condition is among the least satisfactory of the relatively common congenital heart lesions Abbott[1] found an incidence of 5 per cent in an autopsy series of 1000 cases of congenital heart disease, as compared to an incidence of 8 per cent of tetralogy of Fallot

One-fourth of the infants with transposition die in 1 month, and more than three-fourths are dead by the end of 1 year The basic defect is that the left ventricular output (through the pulmonary artery) returns to the left atrium, and blood leaving the right ventricle (through the aorta) returns to the right atrium Basically, therefore, the systemic and the pulmonary circulations are anatomically separate Accordingly, there must, of course, be some point of communication between the two, so that venous blood may enter the pulmonary circuit and arterial blood may enter the systemic circuit This is commonly achieved through either an interventricular or an interatrial (less commonly, both) septal defect Regarding life expectancy, those children with an interventricular septal defect have the most favorable outlook, and those with a combination of both defects the best outlook of all Nevertheless, few indeed of these children live beyond childhood and, as mentioned above, three-fourths are dead within the first year of life

A variety of shunt procedures have been attempted, including the establishment of an artificial interatrial defect, but so far the surgical treatment has been relatively unsuccessful The clinical findings leading to the diagnosis were outlined by Taussig[150] and one of the more extensive early attempts at corrective surgery in such patients was reported by Hanlon and Blalock[76] In 33 patients three types of operations were attempted These included some type of extracardiac venous or arterial shunt, the creation of an atrial septal defect, and a combination of these two methods In the first 28 patients operated upon there were 22 deaths Nevertheless, the last several years have witnessed great strides in the surgical management of congenital heart disease, and this defect may in the future be corrected with operations yet to be devised

The Peripheral Vessels: Pathophysiology and Therapeutic Principles

The first section of this chapter dealt with the general physiology of the circulation, and it was emphasized that the three basic factors which maintain a normal blood pressure are the pump (heart), something to pump (blood volume), and something to pump against (peripheral vascular resistance). The following discussion will be concerned with the pathophysiology of the blood vessels themselves Although certain diseases are of particular importance in producing alterations in the blood pressure, there are specific diseases of the blood vessels which do not necessarily have a particular effect upon the general blood pressure, but they have profound effects upon the functional integrity of the blood vessels in their rôle as conduits for blood flow to the tissues

The Diagnosis of Vascular Disease

THE HISTORY As with most clinical conditions, a careful history of the onset, character, and subsequent course of peripherovascular disease is often of much assistance in reaching a correct interpretation of the pathology Accordingly, it is convenient to begin this section with a review of some of the more outstanding symptoms of peripherovascular disease, followed by a review of

the prominent physical manifestations of vascular disorders. Certain of the more commonly used tests for circulatory dysfunction will then be considered and, lastly, individual diseases will be taken up

Pain. The pain associated with peripherovascular disorders may be mild or it may be most severe, and it is the symptom which most often brings the patient to the physician. While this is more true of arterial disease than of venous disease, it is also a prominent symptom in certain types of venous disease. Of special importance in the diagnostic value of pain are its severity, timing, and the measures which afford relief For example The pain caused by a glomus (vascular) tumor beneath the fingernail may be excruciatingly severe and paroxysmal, coming on particularly when pressure is applied to the fingernail or when the patient experiences abrupt variations in temperatures. There may be little or no obvious change in the circulation of the digit. The pain associated with chronic and progressive arteriosclerosis may at first not be particularly discomforting to the patient but as the disease process continues the pain becomes more constant and boring, occurring particularly at night when he is unable to sleep This relentless inexorable pain in the foot may finally cause the patient to seek amputation. In fact, it is our practice to allow the patient to make up his own mind and be convinced by the pain of the necessity for an amputation, rather than to persuade him against his will if the latter is done he will often be resentful later, for he may feel that amputation was not essential. Still another type of pain is the sudden, extremely severe pain which may be associated with embolism to a major vessel, as at the bifurcation of the femoral artery This pain is usually worse at the beginning (though there are exceptions to this), the leg is cold and sensation may rapidly diminish in the lower leg and foot. If the occlusion occurs at the bifurcation of the aorta or the bifurcation of the iliac artery, then the loss of sensation and of power in the distal leg will extend to a higher level The pain which follows arterial occlusion is essentially due to ischemia. In contrast to all of this, some patients have little pain following embolic occlusion, there being principally weakness and numbness of the part. The character of the pain in Raynaud's disease is virtually diagnostic. Causalgia, a "neuralgic" vascular pain, may follow vascular injury

Intermittent claudication is the term applied to the pain or fatigue or cramps which persons with arteriosclerosis or other disease causing diminished blood flow may have on exercise. The pain or tightness or tiredness experienced in the muscles of the part gradually disappears when the person halts and rests. Actually, "tiredness" usually develops first, followed by pain of increasing severity if activity is not halted, further exercise eventually becoming impossible because of collapse of the leg.

The symptoms may affect the distal foot, the arch of the foot, the calf, or the thigh muscles, depending upon the level of arterial occlusion. In order to define the approximate severity of the circulatory deficit and the efficacy of therapeutic measures, it is useful to determine the approximate distance that the patient can walk before claudication discomfort begins. Again, while the initial discomfort of arterial insufficiency may amount to little more than a feeling of fatigue, the symptoms usually progress with the arteriosclerotic process until the patient is disabled. Yet, this may be long in coming We resected the occluded lower aorta of a man who 15 years previously on the advice of his physician, had begun to limit exercise due to arterial insufficiency in the legs Preoperatively he had pain even at rest, but foot pulses were reestablished by homografting, the ischemic ("trophic") changes gradually regressed, and exercise tolerance was good Naturally, with sclerotic changes in the smaller vessels also, blood flow would not permit vigorous exercise.

Rest pain is discomfort due to arterial

insufficiency (ischemia) which occurs even at rest, perhaps being worse at night This is a sinister and ominous symptom, which often precedes gangrene When pain is constant even at rest, the prognosis without successful surgery is very poor

Pain has been used as an illustrative symptom because of its pre-eminent importance, but in taking the history many other types of information should be sought The character of the onset and the progress of the disease will also be shown to be important in diagnosis as specific diseases are taken up later in this discussion

PHYSICAL EXAMINATION *Inspection* The experienced clinician carefully interprets what he hears by way of history and what he sees and finds by way of physical examination, before proceeding to select the laboratory studies which appear to be most likely to provide additional pertinent information in the given case Thus, a careful physical examination is no less important than a careful history in the management of peripherovascular disease To cite a single example, with experience it is usually possible to determine accurately, merely by inspection of an extremity, the probable ultimate prognosis—especially if effective therapy such as arterial homografting is not feasible One of my professors used periodically to make rounds solely by inspecting each patient and then attempting to name the condition for which the individual was being studied or treated—no historical, laboratory, or other data were given him It was often startling to find that this superior clinician had with only his eyes reached a correct diagnosis which the rest of the staff had taken days to achieve To see, one must consciously look for, and in no other field is this more true than in that of peripherovascular disease

The color of the skin often reflects significant facts regarding the state of the circulation of the extremity The color of the skin, disregarding various types of pigmentation, is usually due to the circulation through the blood vessels of the skin The skin color is affected by the *amount of blood* and by the *color of the blood* That is, the less the capillary flow, the greater will be the concentration of reduced hemoglobin in the blood that does pass into the skin—since the tissues will extract the maximum amount of oxygen from the limited amount of blood

It is not necessary to consider in detail here all the changes in color which may occur in various types of vascular disease Let it suffice to say that the extremity in which arterial or arteriolar occlusion has essentially shut off distal blood flow is pale and white If the blood flow is incompletely occluded, however, permitting a small amount of blood to pass through but under diminished hydrostatic pressure, the marked desaturation of the hemoglobin present will result in variable degrees of cyanosis, as noted above

Passive filling of minute vessels—such as that produced by obstruction to the outflow of blood as in femoral thrombophlebitis—deepens the color of the skin and cyanosis may also appear On the other hand, engorgement of the small vessels of the skin may result primarily from excessive dilatation of the small vessels themselves, as in *erythromelalgia* The redness or rubor of erythromelalgia has a different hue, usually, from that which is due to occlusive arterial disease of the extremity in which blood enters the finer vessels under a reduced head of pressure

In a patient we treated who had Raynaud's phenomenon, different fingers were involved to different degrees, and during attacks the color of individual fingers reflected the variations in vascular pathology The most severely involved digits were pale, almost white, and at the tip of one finger there was an anesthetic area in which trophic, inflammatory ("false felon"), and even early gangrenous changes could be seen (Fig 165) Those fingers that were less severely affected were quite pale, and others still less seriously affected exhibited only cyanosis Cyanosis is, of course, to be pre-

ferred to the pallor of advanced ischemia. In summary, the exposure of the hand affected by Raynaud's phenomenon to cold results in a fairly typical train of circumstances. Due to a local hypersensitivity to cold, the excessive contraction of arteries and arterioles may be such that blood flow to the digits stops completely. (This may be demonstrated by a lack of bleeding when the "white" finger is pricked, or by observing the absolute stasis in the capillary loops on finger microscopy, or by plethysmography, oscillometry and arteriography.) If the exposure to cold is prolonged, sensory changes in the finger will occur and it will eventually become anesthetic. In contrast, as the finger is warmed the opposite train of events is observed. As the spasm of the arterioles diminishes and relaxation occurs, the first blood released into the capillary bed is rapidly deoxygenated and a cyanosis results. Thereafter there may be excessive relaxation of the arterioles with dilatation of the capillaries to an unusual degree—the well known "reactive hyperemia" that is probably due to the accumulation of metabolites during the period of anoxia. This is referred to as the 'pink burning' stage of reactive hyperemia.[36, 37] The color of the skin is influenced not only by blood flow but also by temperature. When the circulation to the skin is arrested, cyanosis occurs much more rapidly in warm skin than it does in cold skin, since oxygen is given up more quickly when the skin is warm than when the skin is cold. Moreover, the oxygen requirements of the cooled extremity are less than those of the warm extremity. In the normal subject the venous blood of the forearm can be 'arterialized' if by heating the extremity, great vasodilatation results in an excessive rate of blood flow; under these circumstances the blood gas values of the venous blood approximate those of arterial blood.

The changes in color which occur in occlusive peripheral arterial disease are almost diagnostic and do not commonly occur in the other conditions which will be considered. The extremity with normal blood flow may exhibit some pallor when raised above the level of the heart for several minutes, as compared with the extremity which has not been raised, but the color of the two extremities quickly becomes identical when the elevated extremity is lowered to the level of the unraised extremity. Moreover, there does not occur a reactive *rubor* or hyperemia of the extremity when it is lowered to its usual position. On the other hand, in the presence of advanced arterial occlusion the extremity assumes excessive pallor when elevated for a few moments and then it is likely to assume an appearance of angry, dusky redness (rubor) when it is placed in a dependent position following elevation. This redness in the dependent position does not indicate excessive blood flow but indicates abnormal dilatation and loss of capillary tone for the blood that does enter these vessels. The pallor on elevation is due to lack of a sufficient 'head of pressure.' Moreover, the degree of pallor which occurs serves as some indication of the severity of the impairment of the arterial circulation. (If the pallor on elevation is patchy, it may indicate the occlusion of some digital arteries but not of others.[3]) When the feet are then lowered to a dependent position, normal color may not return to the skin of the lower extremities at the normal rate. If this is prolonged to a period of 45 seconds or a minute, vascular flow in the extremities is abnormal. In general, the greater the length of time required for "normal" color to return to the foot, the greater is the degree of arterial occlusion. If complete arterial occlusion occurs, as from a sudden and massive arterial embolus, the foot remains pale even in the dependent position. Therefore, the fact that redness does develop in the dependent position indicates the presence of some blood flow, but the appearance of redness with associated cyanosis usually indicates an inadequate blood flow. There are exceptions to this, however, as in acrocyanosis or erythromelalgia. In the patient with occlusive peripheral arterial disease,

if there is a constant dusky redness of the feet in the dependent position, a precarious balance between blood flow and tissue requirements exists, and the prognosis without successful treatment is poor

Acrocyanosis, as pointed out, may produce constant discoloration distal to the wrist and distal to the ankles If this is not completely persistent but tends to be so, it may be due to a late stage of Raynaud's disease The condition in which persistent bluish to bluish-red mottling of the skin of the extremities is present is known as "livido reticularis" It may involve the hands and arms or the lower part of the trunk, but it particularly may involve the thighs The livido is made more prominent by exposure to cold [3]

Another type of skin discoloration which may be misleading and may suggest serious peripherovascular disease is that of the brownish changes due to continuous exposure of the legs to an open fire, oven, or closed heater These patients, who have sat very close to the hearth with their legs exposed, are usually females, since the trousers cover the legs of men, the pigmentation may be permanent and ulceration may occur I had previously encountered this phenomenon only in older patients and had considered that it might be due to deficient skin circulation resulting in a slow dissipation of the heat from the stove or fire However, I have more recently encountered it in youngsters in whom there was no particular reason to suspect the presence of inadequate circulation to the extremity

"Stasis pigmentation" accompanies varicose veins or chronic phlebitis and is frequently noted around the ankle, particularly above the medial malleolus Such changes reflect chronic underlying venous disease

Trophic alterations in the skin and its appendages may also result from ischemia, and they justify a cautious prognosis in patients with aortic occlusive disease who are to be operated upon Among these findings are slickness and shininess of the skin, loss of hair, and deformity of the nails These changes may even precede intermittent claudication, but local pain or fatigue on exercise usually comes first Muscular atrophy and the loss of subcutaneous supporting tissue may reduce the circumference of the toes

Palpation The *temperature of the skin* is influenced by an extraordinary variety of circumstances This organ must respond not only to variations in ambient temperature but also to the changes in metabolism within Blood flow is reflexly altered according to the need to lose or to conserve body heat, as was pointed out in the discussion of body temperature regulation Skin temperature is elevated after exercise, a warm bath, a heavy meal, and under many other conditions. Clearly then, if skin temperature is to reflect changes in vascular physiology *per se,* it must be measured under basal conditions and in a constant temperature room (see below)

Information concerning skin temperatures in one person cannot readily be transferred to another, but the paired extremities of the same person can be compared with each other For example, lowered temperature in any particular extremity or digit, as compared with its opposite or other members, may well indicate inadequate circulation to the part In contrast, increased heat in an extremity, in the absence of infection, may indicate increased blood flow through the extremity, such as may be found in the presence of an arteriovenous fistula or a cavernous hemangioma Finally, the changes in skin temperature do not necessarily reflect with accuracy the blood flow to the underlying muscles which are, after all, the source of the pain in intermittent claudication

The *palpation of arterial pulsations* is an extremely important part of the peripheral vascular examination This is because it is readily done and may give information that is diagnostic Every physical examination should include a specific notation regarding the dorsalis pedis and posterior

tibial pulses. If the foot pulses cannot be felt, the popliteals should be examined and, if these are not palpable, then the femorals. Absence of both femoral pulses may indicate aortic occlusion, which may be surgically correctible. Absence of one femoral pulsation in the presence of the other may indicate occlusion of the common iliac artery at its bifurcation on that side, since occlusions frequently involve the bifurcation of a particular artery. Absent arterial pulsations in the legs of a young person, particularly if he has hypertension in the upper extremities, should always suggest the possibility of coarctation of the aorta.

Swelling of the extremity may be due to any of the usual causes of edema (p. 54). However, in peripherovascular disease it may be due to lymphatic or venous obstruction, to the increased venous pressure associated with an arteriovenous fistula, to the patient's holding an ischemic extremity in the dependent position because this lessens pain, to low grade inflammation, and to other causes. Elevation of the leg usually reduces the swelling, regardless of its etiology.

Unequal length of the extremities may reflect the presence of an arteriovenous fistula which existed before closure of the epiphyses, the overgrowth of bone being due to the increased blood supply. The fistula may be a relatively simple one between an artery and a vein, or it may take on the characteristics of a cavernous hemangioma. The condition is usually fairly obvious from inspection and other means of physical examination, but where the lesion is a deep one and does not involve the skin the examiner may conclude that one leg is abnormally shortened whereas, in reality, one leg is lengthened. Arteriovenous fistulas have occasionally been performed deliberately in youngsters for the purpose of causing increased length of a shortened extremity, but the results have not been encouraging. Moreover, the deleterious effects of such a fistula upon the heart would appear to outweigh any advantages it might have in producing increased length of one leg in the growing child. A cavernous hemangioma may involve all layers of the extremity, including muscle and bone.

Arterial spiders may be seen in the skin and are comprised of a body and legs with a surrounding area of erythema.[13] These spiders may be seen to pulsate, and the application of a glass slide to the lesion and proper adjustment of pressure will disclose pulsations in all instances, the blood flowing centrifugally from the central point to the periphery. These defects are generally situated around the face, neck, and upper portion of the shoulders, but they may be found elsewhere. They occur in normal persons, in persons with parenchymatous disease of the liver, and during pregnancy.

Venous stars usually overlie and are tributary to a large vein.[13] They are similar to arterial spiders but blood flows from the periphery of the star centrally, this being the exact opposite direction of flow from that in the arterial spider. Venous stars develop most characteristically when collateral veins are enlarging as the result of deep venous thrombosis, and at times they may be several inches in diameter.

Auscultation. When the presence of an aneurysm or an arteriovenous fistula is suspected, additional important evidence may be obtained by noting on auscultation the character of the bruit, which may be associated with a palpable thrill. The arteriovenous fistula, as with the patent ductus arteriosus (also an arteriovenous fistula) will usually produce both a systolic and a diastolic bruit. In contrast, the bruit which may be associated with an aneurysm, whether the aneurysm be "true" or "false," has only a systolic component in most instances. Additional important diagnostic evidence, as will be detailed later, is that occlusion of an arteriovenous communication by pressure usually results in a slowing of the pulse rate and a narrowing of the pulse pressure during the period of occlusion.

ADDITIONAL METHODS OF INVESTIGATION

Angiography. This procedure has been con-

sidered previously, but a few additional points are applicable here While angiography is an invaluable aid in visualizing arteries in almost all parts of the body, it is not without certain relatively uncommon but often serious hazards It was pointed out that injection of too much of the medium into a carotid artery might, with improper technic, result in fatal brain damage Angiocardiography is also at times poorly tolerated in the presence of pulmonary hypertension Injection of the radiopaque media (which contain an iodide, usually) into peripheral arteries frequently produces severe spasm and, in the presence of relative ischemia, patchy areas of skin and other soft tissue necrosis may be precipitated Aortograms may occasionally result in renal shutdown or, more rarely, in paraplegia

In contrast to the highly valuable information gained from arteriograms, the information gained from venograms is far less helpful in the average case, due in considerable measure to the marked variation or inconstancy of venous channels

HUMAN PLETHYSMOGRAPHY

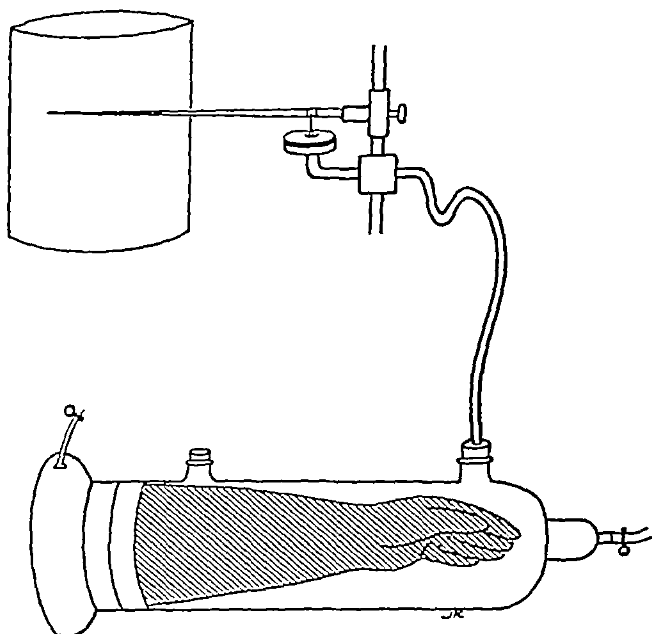


Fig 161 Plethysmography The plethysmograph can be useful in the diagnosis and prognosis of arterial diseases of the extremities It also aids in evaluating the results of therapy It is not often used in day to day clinical practice (After WRIGHT, S *Applied Physiology,* Ed 9 London, Oxford University Press, 1952)

Oscillometry The oscillometer is quite similar to the usual sphygmomanometer, with the exception that it is the excursions of a needle on a dial, produced by the arterial pulsations, that are noted The greater the arterial pulsation, reflecting the stroke volume of blood passing along the artery, the greater will be the deflection of the needle on the scale In our experience, information gained with the oscillometer has added little to that already available from physical examination

Plethysmography The plethysmograph (Fig 161) has been used mainly for the experimental study of arterial and venous physiology, and we have not used it clinically In essence, the apparatus permits the enclosure of a digit or an extremity in a water-filled compartment which is, of course, watertight A cuff is then inflated (the collecting cuff) just proximal to the plethysmograph and the pressure is adjusted to one just below diastolic pressure but above venous pressure, thus trapping the volume of arterial inflow This causes expansion of the enclosed forearm or finger, as the case may be, and the resulting pressure changes within the closed watertight compartment are recorded by a suitable manometer A plethysmograph may therefore be defined as an apparatus for recording changes of volume per unit of time[3] It is a useful apparatus, and the blood flow to the extremity can be rather accurately measured in this way, though it of course does not indicate whether the reduced arterial flow, if present, is due to organic occlusion or to arterial spasm Persistence of a low volume of flow after sympathetic block, however, indicates organic occlusion Actually, if spasm persists long enough, organic vascular changes may occur anyway In Raynaud's disease the diminished arterial flow is due largely to arterial spasm, but in arteriosclerotic disease it is due to organic occlusion In Buerger's disease it may be due to spasm superimposed upon organic occlusion The plethysmograph is often used to determine the effect of sympathetic block

on arterial flow as an indication of the probable value of sympathectomy in the treatment of the patient's condition To repeat, though the plethysmograph is essentially an investigative tool, albeit a valuable one, which is not often essential in clinical practice.

Measurements of skin temperature and reflex vasodilatation. The significance of skin temperature measurements was considered above, including the admonition that the patient must be in a basal state and that the temperature and humidity of the environment must be controlled. Actually, of course, skin temperature changes of clinical significance are often detectable by simple palpation. For example, following successful unilateral paravertebral sympathetic block the involved leg is grossly warmer than the opposite extremity in the person who is capable of vasodilatation If the block was accurate and the extremity does not become definitely warmer it is usually assumed that sympathectomy will probably not improve blood flow significantly

For the actual measurement of skin temperatures various *thermocouples* are available commercially Two thermocouples are usually used one maintained at a constant temperature and the other attached to the skin. When a temperature gradient exists between the two thermocouples, a current flows over a wire connecting the two, causing a deflection of the galvanometer, this deflection is recorded on a graduated scale

Measurements of skin temperature have as their greatest value the reflection of differences between symmetrical parts of the body since usually the temperature of the forehead thorax and thighs is from 7 to 10 warmer than that of the toes There is normally some vasoconstriction of the peripheral vessels of the feet, as indicated by the relatively low temperature of the toes In contrast the temperature of the fingers ordinarily lies within the range of from 32 to 35 C The temperature of the toes exceeds the environmental temperature when the temperature of the fingers rises to between 32 and 35° C, and this usually occurs at a room temperature of from 25 to 26 C (77 to 78 8 F)

Allen, Barker, and Hines[3] have summarized the value of controlled skin temperature as follows

1 A difference of more than 2 C in the temperature of two symmetrical parts of the body almost always indicates impaired circulation Thus if the temperature of the right big toe is 28 C and that of the left big toe is 32 C, it is almost invariably true that the arterial circulation to the right big toe is impaired. The same observation is applicable to companion digits, in the examination for occlusion of digital arteries in the same extremity

2 A sharp change in the temperature of the skin under basal conditions almost certainly indicates a sharp change in a blood flow through the skin For instance if the temperature of the skin of a toe is 28 C under basal conditions and after sympathectomy it is 34 C, it is justifiable to conclude that circulation to the skin has increased markedly Similarly, if the temperature of the skin of a toe is 32 C under basal conditions but somewhat later (as following arterial occlusion) it is 22 C, the conclusion that arterial circulation has been greatly impaired is justified

3 Failure of the temperature of the skin of the fingers to increase to a figure substantially beyond that of room temperature when the patient is moved into a room in which the temperature is maintained at approximately 30 C definitely indicates impaired arterial circulation This is usually (but not always) true of the lower extremities also

Measurements of oxygen tension In a study of experimentally produced immersion foot Montgomery and his associates[114] made a special investigation of variations in oxygen tension of the muscles in the subcutaneous spaces of rabbits' legs exposed to water at 3 C Temperature measurements were also made In general, the tempera

tures decreased to levels characteristic of markedly reduced blood flows, though in some instances there were fluctuations in the tissue temperatures, indicating transient periods of increased blood flow, these fluctuations were observed to persist for as long as 7 days and were apt to be associated with leg motion Usually the oxygen tension of the tissues was depressed by cold, and there was a tendency toward a greater degree of reduction in oxygen supply than in oxygen utilization When the animals were given oxygen by inhalation while the leg was cold, the oxygen tension of the cold tissues rose to or above the level prior to the application of cold

Oxygen tension measurements are not much used in peripherovascular practice

CONCLUDING COMMENT REGARDING TESTS FOR PERIPHEROVASCULAR DISEASE There are various other less frequently used and less practical tests of circulation which may be made Among these are studies of the nailfold capillaries (where arteriovenous shunts are numerous), the measurement of rates of sweating, the rate of clearance of injected radioiodine or radiosodium from the tissues under study, the measurement of skin distensibility, and others However, by way of practical summary, in our experience the history, physical examination, various measurements with the sphygmomanometer, angiography, and differences in palpable skin temperature following paravertebral sympathetic block have been by far the most generally useful and conclusive methods of investigation of arterial disease Tests for venous disease are described in a subsequent section

Immersion Foot, Trench Foot, and Frostbite

EFFECTS OF COLD The writer had a modest experience with trench foot in Army hospitals in England and the United States during World War II, but since then he has had little personal contact with such cases Therefore, Montgomery's[113] review of the physiopathology of immersion foot, as well as the review by Robinson,[120] will be drawn upon in some detail

"The term immersion foot, retained because of brevity, denotes the disorder that results from prolonged chilling short of freezing This loose term seems more satisfactory than 'vasoneuropathy after prolonged chilling' because vasoneuropathy is only part, though perhaps the most important part, of this disorder The term trench foot applies to a similar, but less well defined, condition In this the factors of physical trauma, infection, and occasional freezing are superimposed upon the effects of prolonged chilling, and the term trench foot is customarily used to denote the complications as well as the primary disorder. The term immersion foot should probably be retained to denote only the effects of prolonged chilling, and not the transient effects of brief exposure to cold nor the effects of mechanical trauma that may accompany prolonged exposure of the limb to cold "[113]

A number of factors enter into the amount of chilling which occurs in an extremity Cold air is much less chilling than cold water of the same temperature, but body chilling by cold air may cause such profound vasoconstriction reflexly in a limb that the temperature of the limb may be reduced far more than that of the body and thus render the limb very susceptible to local chilling Sufficient chilling of the body to endanger life is termed cold shock, in which functions of vital organs are dangerously affected (see Induced Hypothermia, p 372 The trunk and its organs tolerate reduced internal temperature less well than a limb does

The changes which occur in a limb exposed to water between 0° C and 15° C are fairly characteristic [113] The skin becomes red and, after a day or more, widespread edema and anesthesia result There is considerable loss of neuromuscular function, but usually gangrene and vesiculation do not appear When these later changes do appear they may be due to mechanical pressure, infection, or intercurrent frostbite Of course, if exposure to the lower temperature is sufficiently

prolonged, pathologic changes may involve most of the tissues of the extremity Whereas previously it was considered that the initial changes occurred in the vessels themselves, more recent experimental studies indicate that damage to muscle and nerves predominates, with some interstitial fibrosis and inflammatory changes in the skin, but with lesser vascular changes

The primary fault in pure immersion foot appears to differ sharply from that in frostbite. *Immersion foot* is a widespread inflammatory process without thrombotic ischemia or true gangrene, *frostbite*, on the other hand, results in necrosis and gangrene and does so both by reason of the direct damage by cold and freezing and by thrombosis which follows shortly after the process of thawing.

Effect of cold on blood flow and on temperature of limbs It is the circulation to the limb that protects against the injurious effects of external cold. Sir Thomas Lewis[103] studied the circulatory responses in the skin of the chilled hand by attaching a thermocouple to the skin of a finger and immersing that part in cold water It was found that the lower the skin temperature, the redder was the skin He demonstrated a rhythmic increase in skin temperature which usually began within 5 to 10 minutes after immersion, diminished in magnitude progressively with time and lasted for the 2 hour period of the experiment. It was assumed that the fluctuations in temperature were a result of fluctuations in blood flow in the skin of the chilled part. Most of the phasic dilatations lasted for between 10 and 30 seconds. It was further shown that the pain in a finger that is exposed to cold is relieved during phasic vasodilatation unless vasodilatation is sudden and that nerve section and sympathectomy did not inhibit the phasing since nerve degeneration did inhibit the phasing it was surmised that the phasing was dependent upon an axon reflex. Lewis further noted that phasing in a limb decreased or failed when the body was poorly protected from cold. Other studies later suggested that arteriovenous anastomoses were responsible for these rhythmic changes in blood flow They opened at 15 C and below The relaxation was occasional at 15 C, frequent at 10 C, and constant at 5° C Responses of capillaries were slower than those of the arteriovenous anastomoses. However, none of these studies was sufficiently prolonged to permit the development of immersion foot. In summary, this phasic dilatation appears to afford some protection against frostbite, and it is probably an important factor in acclimatization to cold. It may also have a bearing upon the problem of immersion foot.[113]

There is convincing evidence that body warmth has much to do with the maintenance of circulation in an extremity exposed to cold. A heavily dressed person at rest in air at −25 C for from 2 to 3 hours requires the best possible mitten to maintain a comfortable hand (i.e, a skin temperature of 15 to 30 C) in contrast, on strenuous exercise no mitten is required, since the body heat production during exercise prevents severe chilling of the hand.

Effect of cold on nerve and muscle Nerve dysfunction and later prolonged damage to peripheral nerves and to sympathetic fibers are a regular part of severe clinical immersion foot. The anesthesia, motor weakness and muscular atrophy which develop may last for many weeks. Since the integrity of the nerve may be necessary to support the phasic increases in blood flow that would be expected to protect the part from cold as previously discussed, it is of importance to know the length of time required for cold to cause sufficient nerve damage to prevent this axon reflex. Bickford[23] found that conduction was altered when the ulnar nerve of man was chilled for brief periods by passing brine through a lead pipe on the skin over the nerve. When the cooling solution was at 3 C the sensations of tickle and of cold were lost Actual motor weakness resulted from a temperature of 0 C, and diminished sensations of "first pain" and of touch from a temperature of −2 C Sensa-

tions of "second pain" and warmth were retained at slightly cooler temperatures Vasodilatation in the skin of the hand, presumably permitted by interruption of sympathetic fibers along the nerve, was effected by a cooling temperature of 0° C It was found that recovery of all functions of the nerve was prompt on rewarming

Microscopic studies have been made of the nerves of cats following exposure to cold solutions The large peripheral nerve fibers were found to be more vulnerable to cold than the small ones While mild grades of damage were shown to be promptly reversible, it was apparent that nerve trunks are readily damaged by cold

Edema in response to cold Edematous swelling is a characteristic finding on exposure to cold, as it is in response to a burn It is further increased by a dependent position of the extremity and by a constriction above The edema fluid has a relatively high protein content, and it is felt that the edema is largely a result of inflammation resulting from damage by cold

Changes in metabolism on chilling As was seen in the discussion of induced hypothermia, oxygen utilization is greatly decreased in the chilled extremity Montgomery and his associates[114] studied the effect of cold on the function and structure of muscle Immersion foot was produced in 107 rabbits by exposing their left hind legs to water at 3° C for times varying from 8 to 64 hours Functional changes resulted and these included inability to spread the toes, inability to dorsiflex the foot, inability to hop normally, and decreased ability to bear weight on the left hind leg Pathologic changes occurred in the muscle and these included basophilia, cellular infiltration, giant cell formation, fragmentation, abnormal variation of the size of muscle bundles, and edema Furthermore, the degree of functional and pathologic change varied directly with the time of exposure There was an abrupt increase in both pathologic and functional changes after 30 hours of exposure There was also suggestive evidence that oxygen administration during exposure suppre[ssed] the functional changes, particularly of [those] exposed to cold water for 30 hours Howe[ver] there was no evidence that oxygen breat[hing] modified the morphologic changes in mus[cle]

CLINICAL CONSIDERATIONS IN COLD INJUR[Y] It has been emphasized that whereas [cold] injuries are more commonly attendant u[pon] military operations, such injuries are by [no] means rare in persons in civil life who [may] be suddenly exposed to frostbite or imm[er]sion foot as a result of a cyclone, flood[, or] occupational hazard This danger is [in]creased if the person exposed has an app[re]ciable degree of peripheral arteriosclero[sis] As has been pointed out, the tissue dam[age] is due less to a direct effect of cold on [the] tissues than to changes resulting from eff[ects] upon the circulation Vasoconstriction, va[so]dilatation, sludging of blood, and thromb[o]sis diminish the circulation bringing warm[th] and oxygen to the extremity The feet [are] particularly vulnerable because they usua[lly] exhibit a temperature which is lower th[an] that of the rest of the body and becau[se] they are usually in a dependent position T[he] injury is further aggravated by immobil[ity] (commonly observed in troops pinned do[wn] by enemy fire) which favors sludging [of] blood, and the injury may also be aggravat[ed] by walking when the oxygen supply to t[he] extremity is diminished

There exists a pronounced difference [in] the ability of different patients to withsta[nd] exposure to cold and even in the same pers[on] at different times, as indicated by the fa[ct] that both the ingestion of food and exerci[se] tend to cause increased body warming [In] exposed persons the temperature, durati[on] of the exposure, humidity, and wind veloci[ty] are also factors which have an effect It h[as] been pointed out that advanced age, po[or] general physical condition, high cold aggl[u]tinin titers, belonging to a dark skinned rac[e] and having had a previous frostbite decrea[se] resistance to cold injury and should be tak[en] into account in an effort to prevent such i[n]jury

Naturally, it is preferable to prevent fros[t]

bite or cold injury rather than to treat it, when possible. However, it has been estimated that only about 50 per cent of those who incur cold injury had warning symptoms of sufficient severity to attract attention. Such patients may complain of feeling cold, of a stinging pain, and of numbness in the involved part. Attempts to "wake up the foot" by sharp exercise under these circumstance only leads to greater subsequent tissue damage. To remove the shoes because of pain in the feet may allow rapid swelling to the extent that the shoes cannot be got back on, with still further exposure and damage. As is well known, exposure to cold in high altitude flying is often associated with anoxia, which further aggravates the injury.

Effect of therapy on cold injury. Minor grades of cold injury usually subside rapidly. Unfortunately, as was learned during World War II, it is frequently most difficult to determine initially what degree of cold injury is present. Some extremities are painful for months following what had originally appeared to be a relatively minor cold injury. In England in 1944 this problem raised the difficult question of whether to return the soldier to duty or evacuate him to the United States.

Isaacson and Harrell[95] studied 33 patients believed to have had bilateral equal injury. Unilateral sympathectomy was performed so that each patient could serve as his own control. Sympathectomy did not prevent or limit the extent of gangrene when performed early, nor did it hasten healing once gangrene was established. Furthermore, it did not protect the extremity against repeated cold injury. Its greatest usefulness appeared to be in the treatment of the late sequelae of frostbite, where it did permit healing of chronic ulcers, relieve paresthesias and pain, and improve the circulation.

Emergency treatment of cold injury. The questions of the rapidity of rewarming and of the temperatures to be used in this process are still a subject of some debate. All agree, however, that excessive heat is to be avoided, though in animals rapid rewarming has resulted in less gangrene than has gradual rewarming. Water is a better conductor than air and rapid rewarming is best achieved in a water bath. Recommended water temperatures range from 98.6 to 108 F. Once the part has been rewarmed it is left exposed to room air, and it is the consensus that massage and pressure dressings are to be avoided. Since smoking causes more or less generalized vasoconstriction, it too should be avoided. The value of anticoagulants and of vasodilator drugs in acute frostbite has yet to be proved, despite some favorable reports.[139] Cortisone has not been beneficial experimentally.

The patient is of course kept at bed rest to diminish further trauma to the tissues of the feet, and excisional surgery is withheld until all possibly viable tissue has been given every opportunity for recovery. There is a notable tendency in this condition for the clinician to overestimate the probable ultimate extent of gangrene.

Raynaud's Phenomenon and Raynaud's Disease

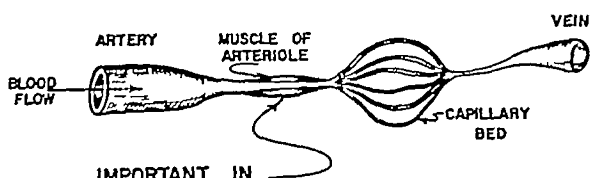
DEFINITION AND DELINEATION OF RAYNAUD'S PHENOMENON. The vasospastic changes which occur in the digits of certain susceptible persons have been the subject of much confusion and misdiagnosis. Originally, Maurice Raynaud described a poorly delineated group of conditions that were discussed in his inaugural thesis for the Academy of Medicine; this thesis was published in 1862 and was entitled "De l'asphyxie locale et de la gangrène symétrique des extrémités."[137] In his writings Raynaud clearly described the attacks of discoloration of the digits which came to be known variously as Raynaud's disease, Raynaud's syndrome, or Raynaud's phenomenon. He considered that the episodes of discoloration of the skin of the fingers on exposure to cold were the result of increased sensitivity of the sympathetic nervous system, and he maintained that it was possible to have gangrene without organic occlusion of either arteries or veins. Unfortunately, he included in his original

description a number of conditions which were not due to purely spastic phenomena, and this led to much confusion regarding precisely what the condition he had intended to describe should be called It has become common practice to refer to the purely spastic disease as *Raynaud's disease*, differentiating more carefully other conditions which may result from arterial occlusion with a superimposed *spastic element* (*Raynaud's phenomenon*) If pure spasm (Raynaud's disease) persists long enough, organic changes may be produced in the walls of the involved vessels

The physiologic basis Typical of most instances of Raynaud's phenomenon is an increased sensitivity of the digital vessels of the individual to cold Exposure of the normal person to cold leads to a lower temperature of the fingers because the digital vessels contract and finger blood flow is much reduced However, unless this is greatly prolonged or unless definite endothelial damage and thrombosis ensue, the reduced blood flow is still sufficient to maintain tissue metabolism in the finger Characteristically the finger becomes pale and perhaps somewhat cyanotic, but it is not white and anesthetic In marked contrast, in the presence of Raynaud's phenomenon there is excessive contraction of the arteriolar walls in the finger when the hands are exposed to cold, and this is of such magnitude that blood

THE ARTERIOLE

ARTERIOLAR TONE REGULATES CAPILLARY FLOW IN VARIOUS ORGANS



1 RAYNAUD'S DISEASE
2 VASOSPASM IN OTHER CONDITIONS
3 EFFECTS OF HYPO AND HYPERTENSIVE DRUGS
4 REFLEX VASODILATION

Fig 162 The arterioles play prominent rôles in conditions such as pulmonary hypertension, systemic hypertension, and Raynaud's phenomena

flow through the fingers may stop completely This excessive contractio termed by Lewis[103] the "local fault may be demonstrated clinically by th of bleeding when a "white finger" is pr or by observing the absolute stasis i capillary loops on finger microscopy I plethysmography, oscillometry, and a ography confirm the completeness o digital artery occlusion If the vasosp ischemia is prolonged, the finger aches, sory change occurs, and finally it bec anesthetic to pinprick

Warming of the hands or finger per relaxation of the artery (Fig 162), and first blood that enters the small ve of the finger becomes rapidly deoxygena This is referred to as the blue cyanotic st Eventually relaxation is excessive, and familiar reactive hyperemia (pink burn stage) that is probably due to local accun lation of metabolites during asphyxia pears, as was described previously

There has been considerable disagreem as to whether the increased sensitivity caused by overactivity of the sympathe nervous system or whether the increas spasm of the arterioles is caused by the loc influence of cold upon these vessels It nc appears from various prolonged studies b many workers that both of these facto apply That is, the narrowing of the norm and abnormal digital vessels is due to th direct local effect of cold and also to an in crease in the vasoconstrictor impulses of th sympathetic nerve supply brought on by body cooling, pain, or emotion For example attacks of Raynaud's phenomenon can be precipitated by cooling of the extremities after an adequate sympathectomy, though the exposure has to be more prolonged than before the operation Of the two factors, Jepson[86] believes with Sir Thomas Lewis that local cooling causing precipitous overcontraction of the arterioles is the more important

Clinical findings In Figure 163 is shown a classification of conditions which may be associated with Raynaud's phenomenon

Again, Raynaud's disease is that instance of the phenomenon which is on a purely spastic basis without underlying organic vascular changes. Clearly, *if organic narrowing is already present, a normal degree of spasm may render the finger ischemic.*

The typical patient with *Raynaud's disease* is a young woman, since the incidence of Raynaud's disease in women is almost five times that in men. Most often the symptoms begin during the late teens, 20's or 30's. The patient not infrequently gives a history of various types of vascular disease in other members of the family who may have had excessively cold hands or feet, "dead" fingers, or other evidences of vasospasm. Migraine, Raynaud's phenomenon, and hypertension are frequently associated and suggest at least some common inherent factors.[3]

The patient usually experiences the attack of painful blanching of the fingers—particularly the tips of the fingers and distal phalanges—on exposure to cold. This need not be excessive cold, but it is excessive for the person in question. It has been mentioned previously that the patient may develop attacks of Raynaud's phenomenon in association with emotional upsets, but emotion is a very poor second to cold as an initiating factor.

The color changes usually begin gradually, but they may come on dramatically with an acute episode of pallor in one or two fingers on exposure to cold—the so called "dead finger" phenomenon. As a rule the tips of the fingers of both hands are involved but later this may extend proximally up the fingers even at times to include the hands. The three phases of color change—pallor, cyanosis and rubor—have been described above. Pain may not be a prominent feature during the attacks but paresthesia is frequently present during the attack and is manifested by numbness, tingling, burning, a feeling of tightness, "pins and needles" or "sticking" in the fingers. Diminished sensation in the involved fingers is frequently prominent and actual necrosis of the tips of the fingers may, rarely, occur. Attacks may increase both in frequency and in severity, so that the patient may be considerably disabled.

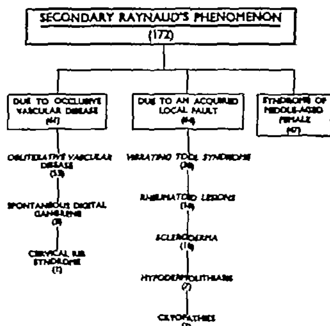


Fig. 163. Raynaud's phenomenon occurs in a variety of conditions other than Raynaud's disease *per se.* (From Jepson, R. P.: Raynaud's phenomenon—A review of the clinical problem. Ann. Roy. Coll. Surg., 9: 35, 1951.)

The *differential diagnosis* of Raynaud's disease lies chiefly in ruling out the other conditions shown in Figure 163. It is apparent that "Raynaud's phenomenon" may represent pure "Raynaud's disease" or that it may represent spasm superimposed upon organic arterial disease (the true Raynaud's phenomenon). It is a common error to diagnose early scleroderma as Raynaud's disease and there are of course numerous conditions which cause morphologic arterial changes in the fingers. Jepson[44] prefers a clinical classification (Fig. 163) which employs primary or true idiopathic Raynaud's disease and "secondary" Raynaud's disease (at times, Raynaud's phenomenon) that is superimposed on or secondary to three main groups—arterial occlusive vascular disease, an acquired "local fault," and the "syndrome of the middle-aged female." He points out that any case of Raynaud's phenomenon occurring after the age of 20 in a man, particularly if symmetrical in distribution, is almost certainly not of the idiopathic vari-

ety and is a secondary phenomenon The secondary Raynaud's phenomenon which is due to occlusive vascular disease may be caused by obliterative arterial occlusion, spontaneous digital gangrene, or cervical rib syndrome Those due to acquired local fault may be caused by the vibrating tool syndrome, rheumatoid lesions, scleroderma, or cryopathies The third group, that of the middle-aged woman, is one which Jepson considers to have been previously poorly or inadequately defined The precise etiology is still not clear, since it occurs too late to be primarily inborn, and there is no evidence of diffuse atherosclerosis The one feature which is relatively common is that it occurs near the menopause and that re-establishment of the menses has often been associated with an improvement in the condition

TREATMENT OF TRUE RAYNAUD'S DISEASE (IN CONTRADISTINCTION TO RAYNAUD'S PHENOMENON SUPERIMPOSED UPON ORGANIC DISEASE)

Conservative therapy The attacks in Raynaud's disease may not be severe and conservative therapy may suffice for long periods of time If possible, the patient should avoid cold weather If this cannot be accomplished, the patient should wear warm clothing at all times and should wear warm gloves and shoes to prevent chilling of the body or the extremities It has been seen previously that chilling of the body may result in a marked spasm of the arterioles of the extremities Obviously, chilling of the extremities themselves will result in arterial spasm in these persons and, indeed, to a lesser extent in most normal persons The patient should be reassured that the condition, while unpleasant, is not going to lead to loss of the hands, such reassurance may diminish the frequency and the severity of the attacks Estrogen therapy, as noted in connection with Jepsons' "syndrome of the middle-aged female," may be helpful in women with Raynaud's disease Raynaud himself noted that the phenomenon often might become aggravated when the menses had stopped, only to be alleviated when the menses resumed However, Allen, Barker, and Hines[3] emphasize that in the m vanced cases of Raynaud's diseas benefit is to be expected from e therapy They note that Priscoline chloride, given orally in doses of fro 50 mg three or four times daily, i helpful in mild cases but that it is n ticularly successful in the more sever

Various other types of medical t have been used, but in general the not been effective in the severe case prolonged therapy in the less severe

Operative treatment Cervical symp tomy is still the method of choice treatment of Raynaud's disease Aft servative measures have been tried w sufficient success over a period of s years—and perhaps trophic changes sibly with scleroderma, are beginning pear due to the chronicity of the co through repeated winters—sympathe may be considered It is not to be perf in all cases, particularly in those whi mild, for it is not uniformly succ moreover, the relief achieved even in able cases may not persist

The type of sympathectomy to b formed has been the cause of much con and debate The reason that this aros that there appeared to be an increase sitivity of the blood vessels of the ha injected epinephrine (and, presumab epinephrine formed by the patient's adrenal glands) following removal o sympathetic ganglia There is, unf nately, much variation in the sympa distribution to the arm, and it is becc increasingly apparent that it may b possible in some patients complete sympathectomize the upper extremity example, in some instances it appears sympathetic fibers may not go to the pathetic chain but may go directly through the spinal nerves Regardless, it has been so difficult to prove beyon rious question that actual hypersensit does occur following removal of the sy thetic ganglia (in contradistinction m to section of the preganglionic fibers e

ing from the spinal cord to enter the thoracolumbar sympathetic series of ganglia) it is probable that other reasons must be sought for the failure of sympathectomy to relieve vasospasm in the upper extremity

In any event there is a firm trend toward resection of the middle cervical (stellate) ganglion, plus the first, second and third thoracic ganglia and their connecting sympathetic trunk

Reasons for failure of sympathectomy in Raynaud's disease Even when it is certain that the condition for which the sympathectomy was performed was pure Raynaud's disease—and not some other condition such as thromboangiitis obliterans, cervical rib syndrome or scleroderma—there are still definite treatment failures from sympathectomy These have been classified into early and late relapse following operation. The early relapses were further classified by Jepson into a group in whom sympathectomy had apparently been complete and one in whom it had not. Relapse after incomplete operation would not truly be called a relapse. However, there are instances of definite relapse within the first few weeks following the operation, when by all available tests the sympathectomy appears to have been complete. It would seem that this most commonly occurs in patients with severe Raynaud's phenomenon, and in this group it is considered that the local fault" was so great "that removal of neurogenic vasoconstrictor impulses was insufficient to allow the hand to retain an adequate circulation even in moderate degrees of cold." There was no evidence that this was due to epinephrine sensitivity The finding was permanent and did not become less marked as the epinephrine sensitivity diminished months or years postoperatively Furthermore the intravenous injection of adrenolytic agents failed to raise the finger temperature in the cases studied by Jepson

In the late relapses the clinical findings occurred months or years postoperatively and the patient's symptoms returned to their preoperative severity Those fingers which were most susceptible to Raynaud's phenomenon preoperatively relapsed first, followed over varying periods of time by the remaining fingers Rather than to believe that actual regeneration of the excised sympathetics occurred in most of these cases, Jepson considered it more likely that alternative sympathetic pathways were present and could not be removed by sympathectomy originally These alternative pathways later came to be utilized in conducting efferent impulses to the vessels and under these circumstances it was not possible to completely and permanently remove all sympathetic innervation of the extremity Simeone and Felder[140] believe that both regeneration and spinal nerve alternative pathways are important

In summary, those cases which are most likely to relapse are those who had severe disease in the beginning and in whom the local fault was strongly developed Late relapse may be due to the regeneration of sympathetics in a few to the alternative sympathetic pathways in many In the occasional case relapsing without any evidence of neurogenic activity, it is probable that the nervous control of the arterial spasm was relatively unimportant initially and that the local fault or local sensitivity to cold—the autonomous intrinsic behavior of the digital artery—was the most important factor in the disease

Cause of Pain in the Upper Extremity

THE SCALENUS ANTICUS SYNDROME If the condition commonly termed "scalenus anticus syndrome' or cervical rib syndrome" is confusing to the medical student, it is hardly less confusing to the practicing surgeon For example a cervical rib may be present with no symptoms or a cervical rib may be present but is apparently not the cause of the symptoms. The scalenus anticus muscle may or may not be the cause of the symptoms Actually there are a number of lesions which may cause shoulder arm or shoulder arm hand pain (Table 18) Among such conditions are osteoarthritis,

TABLE 18 LESIONS THAT MAY CAUSE ONE OR MORE ELEMENTS OF THE "SCALENUS ANTICUS" SYNDROME

1	Scalenus anticus syndrome
2	Diaphragmatic referred pain
3	Cervical disk (herniated)
4	Cervical osteoarthritis
5	Fibrous band from first rib compressing brachial plexus, subclavian artery, or both
6	Cervical rib
7	Anomalous artery compressing brachial plexus
8	Subdeltoid bursitis
9	Rupture of supraspinatus tendon
10	Aneurysm of subclavian artery
11	Spinal cord tumor
12	Superior sulcus tumor
13	Sudeck's phenomenon from trauma
14	Shoulder-hand syndrome following myocardial infarction
15	Brachial plexus neuritis
16	Neoplasm of brachial plexus (*e g* , as in neurofibromatosis)
17	Raynaud's disease
18	Buerger's disease

protruded cervical intervertebral disc, fibrositis and myositis, syringomyelia, spinal cord neoplasm, superior sulcus (Pancoast) lung tumor, brachial neuritis, myocardial infarction, peripheral nerve neoplasm, ruptured supraspinatus tendon, subdeltoid bursitis, thromboangiitis obliterans, and Raynaud's disease, in addition to the more obvious conditions such as cervical rib compression, spasm of the scalenus anticus muscle in the absence of cervical rib, and aneurysm of the subclavian artery An anomalous fibrous band may also compress nerves of the brachial plexus or the contributing nerve roots, moreover, in some patients the scalenus medius may cause more compression than the scalenus anticus [124]

The diagnosis of the scalenus anticus syndrome or of the cervical rib syndrome consists, first, of the symptomatology and physical findings which lead to roentgen examinations and other suitable diagnostic measures As a rule, evidence of compression will come from either the blood supply or the nerve supply to the arm There may be some diminution in the pulse and blood pressure on the involved side On rare occasio there may be sufficient arrest of circulati to cause swelling and edema of the arm ar in extreme instances, even gangrene The may be paresthesia and even anesthe involving the fingers and hand, which eve tually is of course associated with tropl changes involving the thumb and the inte osseous muscles Raynaud's phenomen may be a prominent feature of the sy drome Exaggeration of the compression the subclavian artery may be produced l elevating the arm over the head and som what posteriorly, further abetted by turni the head to the opposite side Such a moti may cause pain or may obliterate the radi pulse, strongly suggesting the possibility the scalenus anticus syndrome Angiograpl may show evidence of an aneurysm of tl subclavian artery which could also produ the shoulder-hand pain

The successful management of the con dition will depend upon accurate diagnosi If the syndrome is due to a taut scalen muscle, the injection of procaine may relie the spasm and temporarily relieve the syi drome Stellate ganglion block may be en ployed However, in the more persiste cases operative exploration may be require Anomalous minor arteries are divided whe they may be compressing the nerve roots, cervical rib is excised, a compressing sc lenus medius or scalenus anticus may l divided at its insertion Again, however, ac curate therapy depends upon accurate diag nosis, so many are the conditions which ma cause shoulder-hand pain The persiste paresthesia, hyperhydrosis, and pain i the hand with trophic changes in the minc muscles of the hand may well be due t coronary occlusion, and it is generall termed the "shoulder-hand syndrome" Th condition, which may be quite disabling, ha responded to cortisone therapy in a numbe of instances It is apparently due to a sym pathetic reflex mechanism

THROMBOANGIITIS OBLITERANS (BUERGER' DISEASE) [3] *Definition* Thromboangiitis ob literans has been defined as a segmental, in

lammatory, obliterative disease of the arteries and veins, occurring almost exclusively in young and middle-aged men, it involves the extremities, and, rarely, the viscera as well. It produces ischemia of the tissues and frequently gangrene. The condition was first described in 1879 by von Winiwarter, who reported a condition which he termed "endarteritis and endophlebitis of the leg" in a 57 year old man who had had symptoms for 12 years. Careful pathologic studies of the arteries and veins of the amputated lower part of the leg, which did not heal for several months, were obviously characteristic of the usual findings in thromboangiitis obliterans. There is evidence that typical cases had been observed even earlier. Even so, the various findings in the disease were poorly systematized and delineated until Leo Buerger, working at the Mount Sinai Hospital in New York, published in 1908 his first paper, entitled "Thrombo-Angiitis Obliterans: A Study of the Vascular Lesions Leading to Presenile Spontaneous Gangrene." In 1924 he published in monograph form a far more detailed report in which he described the giant cells and purulent foci in the occluding vessels. His studies led him to conclude that the disease started as an acute inflammation of the vessels that resulted in the formation of thrombi; he did not emphasize the intimal thickening which has since become recognized as characteristic of the disease.[13]

Pathology. Thromboangiitis obliterans is primarily a disease of the blood vessels of the extremities, involving the lower extremities more commonly and usually more severely than the upper extremities. It has also been found in the viscera and has on occasion led to coronary occlusion. Typically the disease begins in medium sized or small arteries and these may be the only ones affected. The arteries most often seriously involved are the anterior and posterior tibial arteries and the radial, ulna, palmar, plantar and digital arteries. The larger arteries are much less often affected, and involvement of veins is less prominent than involvement of arteries, though a "migratory phlebitis" may precede demonstrable arterial disease. When veins are affected it is usually the smaller or medium sized veins, large venous trunks being rarely attacked.

The characteristic pathologic finding is an inflammatory, nonsuppurative panarteritis or panphlebitis with associated thrombosis but without necrosis of the wall of the vessel. When the veins are affected the characteristic migratory phlebitis may be observed in superficial veins, first one extremity or one part of the extremity is affected, and then another site, with subsidence of the first. Once the vessel is thrombosed it becomes organized by fibroblasts. As in other instances of thrombosis and occlusion, some degree of recanalization may later occur. The pathologic involvement of a particular vessel is not continuous but involves segmental or skip areas, comparatively normal segments of vessel often beginning abruptly just beyond diseased segments. As noted above, different vessels may be involved at different times, but once the disease has produced fibroblastic occlusion of the vessel the occlusion appears to be permanent and is usually complete.[3]

The segmental nature of the occlusion permits considerable collateral circulation and anastomosis to occur. This has been repeatedly demonstrated by arteriography in the intact limb (Fig. 164) and by injections of radiopaque material into the arteries of amputated extremities. As is to be expected, the progressive diminution of blood flow to the involved extremity results in atrophic and later gangrenous changes which usually first involve the toes or fingers, moving proximally progressively, particularly if the individual will not stop smoking. Infection associated with the gangrene contributes considerably to the disabling potential of the occlusion and further diminishes the nutrition of the involved part. The degree of disability caused by thromboangiitis obliterans depends primarily on the degree of arterial occlusion which it produces and



Fig. 164. Buerger's disease with superimposed Raynaud's phenomenon, arteriogram. This 45-year-old man, an inveterate smoker, had had a myocardial infarction a number of months prior to hospitalization for extreme pain due to ischemia of the tip of the right index finger. Cold weather or the mere gripping of the steering wheel of his car were precipitating causes of numbness, tingling, and pallor in the fingers of the right hand and, to a mild degree, of the left hand. The arteriogram of the right hand shows obliteration or narrowing of various digital arteries.

upon the rate at which this is produced, since a modifying factor of considerable importance is the rate of development of collateral blood supply.

Etiology of thromboangiitis obliterans. The etiology of this condition is unknown. Nevertheless, there are certainly contributing factors which are recognized and which are of much importance. The disease usually appears between the ages of 25 and 40 years and occurs almost exclusively in men. In fact, a diagnosis of thromboangiitis obliterans in a woman is to be viewed with great skepticism (even more so than the diagnosis of Raynaud's disease in a man). This overwhelming preponderance of the disease in men obviously suggests some relationship to the male hormone. The question of racial incidence was long considered important, since many of the early cases had been reported among Jews, but the disease has since been reported in virtually all races.

Smoking has an influence on the vascular system in general,[143] and it has been considered to be a major etiologic factor in Buerger's disease. The large majority of normal persons respond to cigarette smoking with definite peripheral vasoconstriction, lasting from a few minutes to half an hour or even longer, before the blood vessels gradually return to normal. There is usually a rise in systolic and diastolic blood pressure, and an increase in pulse rate of from 5 to 20 beats per minute. Nevertheless, there is much individual variation as regards the effect of smoking on the peripheral vessels, and Friedell[58] reported that men and women are not equally sensitive to tobacco smoke. Using radioactive iodinated serum albumin (RISA) as an indicator of volumetric changes in the peripheral vascular system, he concluded that the maximum degree of alteration in blood volume in the measured extremity in sensitive men averaged 19 per cent, whereas in women who responded the degree of alteration was approximately 33 per cent. The use of a filtered cigarette in each case lowered the responses considerably. The men showed a 10.7 per cent change with a filtered cigarette, while the women showed a 20.5 per cent change.

The general systemic effects of smoking represent, of course, the major factor in the inability of many persons to stop smoking. The "habit" constitutes a physiologic conditioning rather than merely a psychologic routine of "going through the motions" of smoking a cigarette.

There are other measurements which serve to indicate the effects of smoking on the cardiovascular system. It has been shown beyond further question that in persons with disease of the coronary vessels an ECG effect may be produced by smoking a cigarette, and it has also been shown that the

ballistocardiographic complexes in a person with an ischemic myocardium can also be altered. Furthermore whereas the smoking of cigarettes which are devoid of nicotine results in no appreciable effect on the cutaneous temperature of the extremities, there is a measurable diminution of the skin temperature following the smoking of an ordinary cigarette

It has been demonstrated that smoking of one or two cigarettes causes the release of from 3 to 100 milliunits of the pituitary hormone into the blood stream in concentrations sufficient to produce vasoconstriction of the coronary vessels of the dog and presumably capable of having the same effect in man [34] In some persons smoking appears to produce a symptom complex similar to angina pectoris, and it is now appreciated that the drinking of a cocktail does not necessarily abolish the effects of nicotine on the cardiovascular system. Thromboangiitis obliterans is certainly more frequent and severe among persons who smoke excessively than among those who smoke little or not at all

To summarize the relationship between smoking and thromboangiitis obliterans, while it has not been definitely proved that smoking is the primary etiologic factor in this condition, it is rare indeed that thromboangiitis obliterans is encountered in nonsmokers. Thus smoking does constitute a major aggravating factor to say the least And all physicians who have treated patients with Buerger's disease have observed that if the individual will stop smoking the process usually improves that, on the other hand if the individual does not stop smoking other types of therapy are usually not particularly successful and the disease tends to progress to amputation of digits and more proximal portions of the extremities. The writer once assisted in the care of two patients with Buerger's disease each of whom had had upwards of 50 separate operations. Despite repeated infections associated with gangrene of progressively more proximal portions of all four extremities both of these individuals refused to stop smoking until no portion of the hand remained with which to grasp a cigarette

Even so, obviously only a very small percentage of heavy smokers develop Buerger's disease, and there must be other contributing factors, including those which result in the overwhelming and almost exclusive preponderance of this disease in men.

Clinical findings The clinical findings in Buerger's disease are essentially the same as those in occlusive vascular disease from any other cause, perhaps with the exception that the patients are younger than those with atherosclerosis, that infection plays a more prominent rôle, and that the veins are often involved early in Buerger's disease In my personal experience, painful 'migrating phlebitis' has not regularly been a useful clue in differentiating the occlusive arterial disease due to thromboangiitis obliterans from that due to embolism or atherosclerosis If roentgen examination demonstrates calcification of the arteries, then Buerger's disease is unlikely The symptoms of occlusive arterial disease are of course, pain, intermittent claudication and subsequently pretrophic or rest pain later pain is associated with trophic changes and finally ulceration and gangrene appear with osteoporosis and bone atrophy in the involved extremity In contrast to the pain in the superficially involved veins mentioned above pain along the involved artery is not particularly prominent These patients are sensitive to cold and a secondary Raynaud's phenomenon is not infrequently observed The reason for this increased sensitivity to cold is that partial occlusion of the vascular supply to the extremity is already present Vasoconstriction of a degree which normally occurs in any patient on exposure to cold may sufficiently further reduce the arterial supply to the involved extremity to produce serious ischemia with the appearance of the 'white digit.' In one patient, the pressure on the fingers required for gripping the steering wheel while driving was enough to produce pallor and numbness (Fig. 165)



Fig 164 Buerger's disease with superimposed Raynaud's phenomenon, arteriogram This 45-year-old man, an inveterate smoker, had had a myocardial infarction a number of months prior to hospitalization for extreme pain due to ischemia of the tip of the right index finger Cold weather or the mere gripping of the steering wheel of his car were precipitating causes of numbness, tingling, and pallor in the fingers of the right hand and, to a mild degree, of the left hand The arteriogram of the right hand shows obliteration or narrowing of various digital arteries

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Fig 165 Buerger's disease with secondary or superimposed Raynaud's phenomenon Note incipient gangrene of tip of right index finger The impending gangrene was averted and symptomatic relief obtained by right cervical sympathectomy

The diagnosis of thromboangiitis obliterans The diagnosis consists primarily of evaluating the probabilities which have been listed above, in the presence of demonstrable occlusion of the distal arteries in a younger individual It is often difficult, even where migratory phlebitis is present or there is definite evidence of arterial occlusion, to diagnose the condition accurately The history of the clinical course is frequently helpful, and roentgen examination will usually rule out calcification of the vessels Buerger's disease is characterized by exacerbations and remissions and, particularly if the individual can stop smoking, the attacks may gradually subside and further occlusion and ischemia not appear Biopsy may be helpful

Buerger's disease of the finger, an infrequent finding, may produce the appearance of genuine infection in the distal phalanx, the so-called "false felon " To incise such an ischemic finger is to invite inordinately prolonged healing, if not actual gangrene Heat is also contraindicated, of course One condition which is still confused with Buerger's disease is that of complete or incomplete aortic occlusion in a relatively young person When good femoral pulses are not present, an aortogram should be done before a diagnosis of thromboangiitis obliterans is made

Survey of effective therapy in Buerger's disease Measures to halt progress of the disease —The immediate progress of the mixed ischemia and infection may be improved by the judicious use of antibiotics However, little definitive improvement can be achieved by conservative measures unless the patient stops smoking The position of the ischemic extremity may be adjusted to that which is most comfortable for the individual, since this probably represents the level of optimal blood flow to the part Chilling of either the body as a whole or the involved part should be avoided by the use of warm clothing

Treatment of disease which is present — Vasodilating drugs have, in our experience, produced relatively little measurable or lasting improvement We do use Priscoline in oral doses of from 50 to 100 mg four times daily, and this may produce some symptomatic relief from pain It may also reduce the likelihood of impending ischemic gangrene Nevertheless, this and the many other efforts at vasodilatation have not produced definitive improvement, though they may aid temporarily

Cervical or lumbar sympathectomy is usually of prompt and demonstrable benefit Pain is relieved and ischemic ulcers of the fingers or toes often heal The probable improvement by sympathectomy may be estimated by preoperative paravertebral sympathetic block with procaine, but the absence of definite evidence of vasodilatation following such a block has not deterred us from performing sympathectomy where the ischemia of the toes threatened to result in gangrene In fact, definite trophic changes have routinely constituted an indication for sympathectomy

If actual gangrene is present, conservative local amputation will usually be required Though healing may be slow, it can usually be anticipated with some confidence, in sharp contrast to almost certain nonhealing of conservative amputations in pure arteriosclerotic gangrene of the toes As a rule, sympathectomy should precede amputation of any but obviously gangrenous tissue, the increased blood flow to the part may permit survival of questionably viable tissue

To summarize, the two dependably successful therapeutic measures which may be used in this disease are for the patient to

stop smoking and to perform *sympathectomy* on the involved side. All other measures are symptomatic and produce only temporary benefit. Anticoagulants may be helpful in some cases, specifically, in one patient who had had repeated pulmonary *emboli from* involved leg veins, the embolization was controlled only so long as he was on Dicumarol therapy. Unfortunately, this does little for the basic disease process.

CERTAIN OTHER INFLAMMATORY DISEASES OF ARTERIES. Mention should be made of *periarteritis nodosa, a disseminated arterial disease* of unknown origin characterized by focal inflammatory lesions which involve chiefly the medium sized and small arteries and arterioles, all layers being involved. The clinical manifestations of this condition, which is now grouped among the collagen diseases, are protean, depending upon which arteries to what organs are involved. It has been considered by many to be an allergic phenomenon, possibly due in some cases to sulfonamide therapy. Nevertheless, the cause remains unknown and treatment remains ineffective.

Another interesting arterial disease is that of *temporal arteritis*. The temporal arteries become painful and tender, one or both being involved, the biopsy of the involved vessel exhibits microscopic findings of a granulomatous arteritis. The condition has frequently been found to respond to ACTH and cortisone therapy. These agents appear to influence favorably both the local and systemic systems, and may prevent the visual loss which can occur in this condition. These drugs do not restore vision that has been lost prior to the time treatment was started. The loss of vision is due to occlusion of the retinal artery or the arterioles, or to ischemic optic neuritis.[3]

Arteries may also be involved in inflammatory processes which involve surrounding structures.

Arteriosclerosis Obliterans

The following discussion will have to do with occlusive disease of the lower aorta and more peripheral arteries, particularly

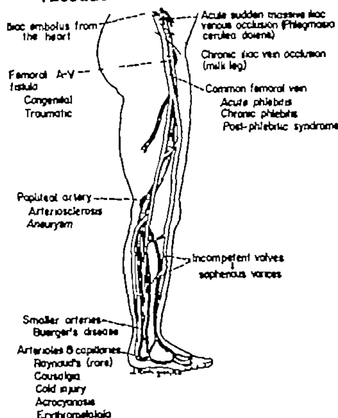


Fig 166 The pathophysiology of most of these conditions is considered in the text.

those supplying the lower extremities, due to what one may loosely term arteriosclerosis (Fig. 166). Actually, atherosclerosis would be the preferable or more exact term for the etiologic definition of most of the circumstances which will be considered. *Arteriosclerosis* has now become the term applied generally to the group of diseases which are characterized by actual structural changes in the medial and intimal layers of the artery and result in loss of elasticity of the artery, in addition to diminishing the size of the lumen. The condition which primarily affects the media, *Monckeberg's sclerosis*, is more immediately associated with the aging process and produces the familiar tortuosity of the visible and palpable larger arteries. In contrast, atherosclerosis, the condition with which this section will be primarily concerned, affects chiefly the intima or the area just beneath the intima, it appears to be due to a mechanism different from that producing medial sclerosis, and it is influenced by a number of factors, including

distal obstruction of the vessel, hypertension, increased dietary lipids, sex, uncontrolled diabetes mellitus, and gout—in addition to the fact that the aging process unquestionably contributes to its complex mechanism of development Increased blood lipid levels, whether or not important in their qualitative aspects, appear to be a significant factor and one which lends hope that the condition can be prevented to some extent by proper dietary management

CLINICAL MANIFESTATIONS OF ARTERIOSCLEROSIS The clinical manifestations of arteriosclerosis are due largely to the narrowing of the caliber or lumen of the vessel Yet, there are certain other complications which may result from disturbed structure of the vessel wall—such as the usual aneurysm of the abdominal aorta, the fairly sudden occlusion which may occur around an atheromatous plaque, or a dissecting aneurysm of the aorta which, also, probably results from the undermining of an atherosclerotic plaque by the force of the blood stream Atherosclerotic changes are manifested particularly in the brain, heart, kidney, and lower extremities The usual process is that of acute or chronic arterial occlusion. Nervous tissue has the least tolerance for a diminished oxygen supply, with renal and myocardial tissues further down the scale, skin and voluntary muscle require the least oxygen of all, certainly over periods of relative ischemia Obviously, certain tissues are expendable whereas others are essential for life

THE DETERMINING FACTOR IN SYMPTOMS As emphasized earlier, the particular clinical manifestations which may be produced in any particular patient will vary widely depending upon the particular artery which is occluded Although atherosclerosis tends to be widely distributed, some vessels are often more severely involved than others For example, coronary occlusion due to atheromatous deposits may occur with little involvement of the vessels of the brain or legs

Cerebral arteriosclerosis may result in a stroke or, at times, quite bizarre neurologic manifestations, coronary atherosclerosis produces angina pectoris, renal involvement may result in hypertension or uremia, occlusion of the abdominal aorta may eventually produce Leriche's syndrome with impotency and perhaps pain in the buttocks or thighs on walking; arterial occlusion in the femoral produces intermittent claudication in the calf, and so on

Ischemic versus neurologic pain Patients with arterial lesions are often referred first to a neurologist or neurosurgeon, and one of our patients whose aortic occlusive disease had for some time been treated for "neuritis" was completely relieved by aortic resection and the insertion of a homograft Arterial occlusions that simulated neurologic disorders of the lower extremities were reviewed by Gilfillan and his associates [61, 62] According to these authors, the veterinarian Boullay first described the syndrome of intermittent claudication as early as 1831, and in 1858 Jean Marie Charcot described lameness and pain of claudication in horses pulling carriages He also described an aneurysm of the common iliac artery in a patient and was perhaps the first to give an accurate and comprehensive survey of the clinical picture of pain due to vascular insufficiency in the lower extremity of man

With the recent surge of interest in the diagnosis and treatment of occlusive disease of the lower aorta and leg vessels, knowledge of the symptomatology of ischemia of certain muscle groups and sensory areas has been increased and further refined *Terminal aortic obstruction* (Fig 167) produces, as mentioned above, a symptomatology which has come to be known as Leriche's syndrome, and is characterized by atrophy of the musculature of the lower extremities including the buttocks, impotency or difficulty in maintaining an erection, and intense fatigue and muscular weakness of the lower extremities When the patient is forced to walk, severe pain may develop in the buttocks, thighs, and legs, often in this order *Total iliac obstruction* may be associated

with pain beginning in the low buttock and extending into the thigh and then to the calf on the affected side The resemblance of such pain to that of nerve irritation at the lower lumbar and sacral levels has at times caused difficulty in making the differential diagnosis. *Partial iliac obstruction* may be associated with a syndrome of pain on exertion which includes a systolic bruit over the involved artery and claudication pain commencing in the calf and ascending to the thigh and buttock secondarily Obstruction of the *profunda femoris* may be associated with pain in the anterior or medial aspect of the affected thigh and obstruction of the *superficial femoral* or *femoral popliteal* vessel causes the common claudication pain in the calf and popliteal area Arterial occlusion in the vessels of the calf may be reflected by claudication pain in the sole of the foot.

PRINCIPLES OF MANAGEMENT OF OCCLUSIVE DISEASE OF AORTA AND MAJOR ARTERIES OF THE LOWER EXTREMITIES. The satisfactory management of occlusive disease of the aorta and major vessels to the lower extremities will depend upon an accurate diagnosis of the etiology and extent of the condition and, in the case of sudden occlusion, prompt therapy

Diagnosis The diagnosis of occlusion of the lower aorta rests upon the historical and physical findings outlined previously These include the temperature of the lower extremities palpation of individual vessels, oscillometric readings, blood pressure readings muscle atrophy and other trophic changes (loss of hair shiny skin, deformed nails) in the lower legs and the use of arteriograms or aortograms Of these the evidence obtained from the *history,* plus careful *physical examination* (including notation of skin color temperature and arterial pulsations) and the arteriogram are in our experience by far the most reliable measures in making an accurate diagnosis

Treatment Until recently the surgical treatment of arterial ischemia of the lower extremities consisted largely of lumbar sym-

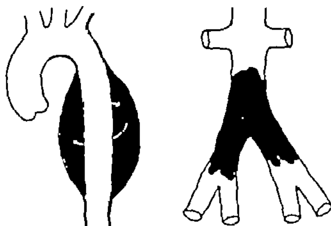


Fig 107 Left Dissecting aneurysm *Right* Occlusion of lower aorta A dissecting aneurysm usually begins in the proximal aorta and progresses downward By moving between the layers the blood tends to occlude the tributaries of the aorta. Atherosclerosis and syphilis, often in association with hypertension are the two most common causes Chronic thrombotic occlusion of the lower aorta producing Leriche's syndrome is caused by atherosclerosis.

pathectomy, followed all too often eventually by amputation At the present time, however, virtually every patient in whom there is the slightest question as to whether or not amputation is avoidable deserves an aortogram if the femoral pulsations are weak or absent. It is only by an acute awareness of the possibility of occlusion of the aorta or the iliac or femoral arteries that proper direct surgical attack will be carried out to restore a lumen of good caliber by either endarterectomy or homografting—for sympathectomy can only *diminish the element of vasospasm,* leaving the more serious organic occlusion unaffected. Neither *sympathectomy nor medical measures can be expected to restore essentially normal flow in occlusive disease of major vessels*

Lumbar sympathectomy has been used for many years as treatment for a variety of diseases of the lower extremities that produce ischemia among these being thromboangiitis obliterans "diabetic gangrene," arteriosclerotic ischemia and cold or other injury with ischemia or causalgia. The indications for sympathectomy in this variety of circumstances were that a degree of arteriospasm was superimposed upon the underlying organic disease a particularly good

example being thromboangiitis obliterans Moreover, sympathectomy was of some benefit in perhaps two-thirds of cases, and it was "curative" in a few Now, however, aortic resection or bypassing has proved vastly more effective than sympathectomy in suitable cases, so much so that the true value of sympathectomy in occlusive disease of major arteries must be candidly reappraised Sympathectomy should probably be used as the sole method of surgical treatment only in those patients in whom there is widespread occlusion of the vessels of the lower legs in the absence of a definite resectable major segment of occlusion such as occurs in the terminal aorta and its bifurcation, or in the iliac and femoral arteries To repeat, sympathectomy can do nothing towards enlarging the lumen of an artery whose stenosis is due purely to organic obstruction, it can only relieve a possible spastic element that is superimposed upon organic occlusion It does provide some measure of improvement in some patients, and we perform bilateral sympathectomy in patients with ischemic pain or threatening necrosis if a more effective surgical attack cannot be utilized Sympathectomy may of course be combined with endarterectomy or with resection of a thrombosed area and replacement with a graft Even so, if an arterial lumen of good size has been restored by removing organic occlusion, division of the sympathetic nerves becomes unimportant in most cases

Resection or bypassing of occluded segment with graft The availability of preserved aortic homografts and arterial substitutes has made possible multiple grafting procedures of diseased arterial segments This has been applied with particular vigor and success to the occlusion of the lower aorta and its bifurcation Patients may not be aware of the disease of the lower extremities for many months following the beginning of the occlusion, but at operation the vessel may be found to be filled with a solid core or plug of organized thrombus which may extend from the renal vessels down to and including the iliac bifurcation on either side Indeed, it may involve the femorals as well but, if it does, successful restoration of good flow is less likely Occasionally the thrombosis extends upward and produces renal failure but, in our experience, thrombosis at this level usually presents as a hillock or mound between the ostia of the renal arteries, permitting continued flow through these vessels When the thrombus extends to the level of the renal arteries, a clamp may be first applied above the renal vessels (or diagonally between the renal vessels to maintain flow to one kidney) and, making an incision across the aorta several centimeters below, by endarterectomy the upper extension of the thrombus can be removed, leaving media-adventitia to which the graft can be anastomosed proximally A second clamp is then placed at a level a distance below the renal vessels and the first clamp (above) is opened but left in place as a safety measure, until the distal anastomosis has been completed By this series of maneuvers the duration of renal ischemia is minimized Of course, one may elect to remove the entire clot by simple endarterectomy, using no homograft or plastic prosthesis Various shunts with tubing may also be used to minimize ischemia, when required

Insidious occlusion of the aorta was brought to the attention of the profession by Leriche[99] in 1940 and was later emphasized by Elkin and Cooper[51] The first resection of the abdominal aorta with homografting was performed in 1952 by Dubost and his associates[49] for aneurysm Since that time aortic resection has become commonplace, due in no small measure to the sound work of DeBakey, Cooley, Creech and their associates

We have abandoned the use of heparin during or following aortic resection If the anastomoses have been correctly performed and the vessels are patent at the end of the operation, clotting is unlikely to occur thereafter and potential hemorrhage due to heparin is avoided The best possible means of

avoiding postoperative thrombosis is to be certain at operation that free distal arterial flow is present, to permit a full head of pressure through the aortic graft into the femoral vessels.

Delayed foot pulses following grafting One phenomenon of considerable concern at times is the fact that foot pulses or even femoral pulses may not be palpable for from 24 to 72 hours following operation—despite the fact that free flow existed at the close of the operation, that the leg appears to be viable, and that excellent pulses may be present subsequently The urgent question is, of course, whether or not to reoperate This phenomenon is due to arterial spasm. The normal femoral artery may be reduced almost to a cordlike structure by spasm in the presence of femoral phlebitis.

Signs of diminishing viability of an extremity following aortic surgery Coldness and pallor of the extremity, with an absence of even femoral pulses, may be due almost entirely to arterial spasm and is, as we have just seen, compatible with viability of the extremity In fact, foot pulses may be excellent 24 hours later How, then, can one know when the extremity is not viable so that the graft can be re-explored before it is too late?

The first evidence of diminishing functional integrity of the leg is loss of sensation to touch or pinprick. Shortly afterward or at times before, the patient will find it impossible to move the toes or the foot as the case may be In particular, if the patient could move the leg or legs immediately following operation but can now no longer do so (especially if movement of the thigh excludes cord damage) the extremity will probably not survive without further surgery Usually the graft will be found to contain clot and, following its evacuation good distal flow can often be achieved Finally, if the technical aspects of good arterial anastomosis are always carefully adhered to, very few patients will require secondary operations.

Selection of cases Aside from imperfect technic, the commonest cause of failure of aortic grafting to preserve the extremity is that of advanced atherosclerotic occlusion of more distal arteries, the same process that precipitated thrombotic occlusion of the aorta In general, if advanced trophic changes and impending gangrene are already present in association with the occlusion of the aortic bifurcation, the results of aortic resection and grafting will usually not save the leg On the other hand, in relatively young patients (in their 50's) who have occlusion of the aortic bifurcation without advanced arteriosclerosis of the distal vessels and trophic changes of the skin and nails of the feet, the improvement following resection of the aorta may be extremely gratifying Patients who previously could scarcely walk across the room without pain and fatigue in the extremities are often able to walk without limitation following operation. Since it is a simple matter to perform bilateral lumbar sympathectomy with the exposure which has been achieved for the purpose of resecting the aorta one can divide these nerves at the time of aortic surgery to reduce postoperative arterial spasm (though we rarely do so)

Thromboendarterectomy This procedure is frequently and successfully employed in connection with occlusion of the aorta and iliac vessels but the success achieved with its use in the femoral and smaller vessels has been limited. The femoral vessels have usually thrombosed following thromboendarterectomy, and at the present time arterial bypassing is preferred by most. Arterial surgery is greatly facilitated by precise localization of points of occlusion and, if indicated arteriograms performed on the operating table are most helpful

In the aorta, it is usually relatively simple to establish a plane of cleavage between the occluding plug (which includes the intima subintimal deposits, and the inner portion of the media) and the outer layer of media with the adventitia

SUMMARY OF MEASURES OF USE IN ARTERIOSCLEROTIC ARTERIAL DISEASE. Although the

above review has been devoted to surgical procedures which may be done, a great many cases of arteriosclerotic occlusion are of such a diffuse nature that, aside from the possible value of sympathectomy, little helpful surgery can be offered Nevertheless, even in these patients something may often be accomplished by a careful program of conservative management Extremes of temperature should be avoided and, most important, the patient should not injure the toes through improper cutting of the toenails He will also maintain strict diabetic control, should he have the disease He should stop the use of tobacco if Buerger's disease is suspected Fungus infections of the toes and feet are treated, and vasodilators can be used for symptomatic relief and in periods of impending gangrene While the results here are not often dramatic, they afford in a great many patients the only measures besides sympathectomy that are likely to be beneficial They should be used with vigor

To conclude, in suitable candidates arterial resection with grafting, thromboendarterectomy, or bypassing with a graft constitutes the most direct and successful means of truly increasing blood supply to the ischemic extremity

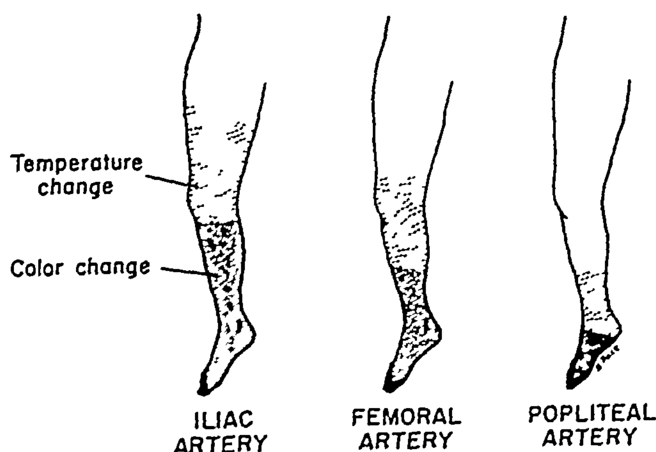


Fig 168 It is useful to note not only the extent of the color change but also the extent of temperature and sensation changes First an ischemic extremity becomes numb, then power is lost, and soon gangrene ensues

Sudden Arterial Occlusion (Embolism and Thrombosis) (Fig. 168)

Sudden occlusion may involve almost any artery of the body, but one of the more dramatic examples is sudden occlusion of the bifurcation of the aorta This is usually due to an embolus from the left heart, producing the so-called "saddle embolus" While some instances of sudden occlusion of major arteries are due to thrombosis, most are due to embolism Of 100 cases studied by Allen, Barker, and Hines,[3] 41 were due to emboli from heart disease, the most frequent source of emboli Although 32 were considered to be due to "thrombosis," it could not be definitely excluded that the thrombosis might not have begun as an embolus secondary to myocardial infarction In patients with atrial fibrillation, emboli may arise from the left atrium Again, *embolism from the left heart constitutes the major cause of sudden arterial occlusion*

The embolus may involve virtually any artery, as stated, but certain arteries are more frequently occluded than are others Emboli tend to lodge at bifurcations Specifically, occlusion of the aortic, iliac, femoral, or popliteal bifurcation is most often encountered However, the embolus may enter the brain or it may enter the superior mesenteric artery and produce gangrene of the major portion of the small bowel and a portion of the colon In contrast, thrombosis most often affects smaller vessels such as the coronary and cerebral arteries

When the patient has atrial fibrillation or has been known to have a recent myocardial infarction, the cause of the sudden arterial occlusion is usually not difficult to diagnose Conversely, the occurrence of arterial embolism should suggest the possibility of myocardial infarction in a patient who is not fibrillating, as in the following instance

CASE STUDY A 54-year-old man with left femoral occlusion was referred to us almost 48 hours after the probable time of occlusion He had had no symptoms particularly suggestive of heart disease, but had had an

attack of upper abdominal pain 2 weeks previously which had been diagnosed as pancreatitis on the basis of an elevated serum amylase level The arterial involvement had occurred while the patient was sitting with the left leg crossed over the right during recuperation from this attack when he wished to uncross his legs he found he could hardly move the left one. Pain developed only slowly and was never severe. Because of the circumstances of onset of the occlusion, we diagnosed femoral thrombosis rather than embolism. The foot was already gangrenous when he arrived at the University Hospital, and the leg was amputated. However, his convalescence from a rapid amputation under minimal anesthesia was inordinately protracted—tachycardia, profuse sweating, mild dyspnea and an ashen color being prominent features even at bed rest.

Since we were not at all satisfied with the *patient's progress, an internist was asked to* re-evaluate the entire case He examined the patient, requested an ECG, and promptly diagnosed massive myocardial infarction with heart failure The use of digitalis and a mercurial diuretic resulted in dramatic improvement.

We had not strongly considered an embolus from the heart because of the following inadequate reasons (1) the absence of atrial fibrillation (2) the fact that the patient was referred with a diagnosis of pancreatitis that was supported by elevated *serum amylase levels* (3) *because of the slow* and essentially silent onset of the occlusion and (4) because pancreatic disease may be associated with vascular occlusion. In retrospect however, the pain of "pancreatitis" was doubtless that of a "heart attack" (as his wife had quietly believed from the beginning) and the only moderately elevated amylase level may have been due to spasm of the sphincter of Oddi following the administration of opiates. All too often one is unduly influenced by a previous diagnosis in a given case especially if the clinical impression was *supported by objective laboratory data* The moral is that one should not accept a previous diagnosis without an utterly independent analysis of the facts of the case. Incidentally, observers who first saw the patient after the occlusion had been misled by the major symptom of paralysis without appreciable pain and, despite marked pallor of the left leg, had for almost 24 hours entertained the diagnosis of a nerve lesion rather than arterial occlusion Paravertebral blocks were then employed for another 24 hours before the patient was transferred for possible arterial surgery Unfortunately, by this time the leg had already turned a dark purple and a line of demarcation had appeared, below which gangrene was obvious

This case emphasizes that, while arterial embolism is usually characterized by *sudden pain in the involved member, this need* not always be so It is at times advisable still to perform embolectomy, even though *the foot may be obviously beyond salvage* Better blood flow to the remaining thigh may allow the stump to heal promptly, where otherwise it might not. In fact, in one patient a subsequent disarticulation of the thigh was required because all the surrounding muscle sloughed following amputation for iliac occlusion Morbidity was enormously increased over what it might perhaps have been had embolectomy been performed even though the foot and lower leg were already gangrenous

More than 50 per cent of involved legs can be saved if embolectomy is performed within 6 hours, though the patient may die of subsequent emboli or of the underlying heart disease *Heparin is not essential post*-operatively

Arterial occlusion may involve arteries which cannot be examined, and a *patient* is described (p 337) who had all the signs and symptoms of an "acute abdomen." Mesenteric arterial occlusion often produces gangrene of variable lengths of bowel before the diagnosis is established, frequently at autopsy

THE DIAGNOSIS OF SUDDEN ARTERIAL OCCLU-

SION FURTHER COMMENT As with most diagnoses, the circumstance which most readily leads to a correct diagnosis of sudden arterial occlusion is the suspicion that the patient has a condition which may have resulted in the release of an embolus—such as atrial fibrillation, a recent myocardial infarction, or generalized arteriosclerosis When the patient has sudden and severe pain, the correct diagnosis is more likely to be suspected than when the onset of the symptoms is characterized by a gradual numbness and paralysis Again, various forms of arterial disease are frequently considered to represent primary nerve lesions for some time before the correct diagnosis is established In a series of patients studied by Allen, Barker, and Hines[3] the symptoms appeared suddenly in only 48 per cent of cases and in only 54 per cent of cases was pain the initial symptom On this basis, sudden arterial occlusion would be suspected in only about one-half of the cases in which it occurs, if abrupt pain were considered the only symptom of importance Equally important, in our experience, are numbness, coldness and tingling, associated with progressive muscular weakness and, later, inability to move the leg at all Of course, the rapidity with which symptoms appear is related to whether complete occlusion occurs abruptly or only gradually

The diagnosis of arterial occlusion in a lower extremity is made on the basis of the symptoms previously mentioned, along with a careful search for confirmatory physical signs of arterial occlusion at various levels and diminished venous filling The value of an arteriogram in defining the level of acute arterial occlusion should not be ignored

Arterial spasm may so closely simulate arterial occlusion that the differentiation may be almost impossible We once were asked to see a patient in consultation in whom the differential diagnosis involved distinguishing acute venous disease from acute arterial occlusion There was no particular reason to suspect that the patient had sustained acute arterial occlusion, since there was no evidence of antecedent heart disease, but it was only after successful paravertebral sympathetic block that relaxation of the artery was effected Here the arterial spasm proved to be associated with massive venous occlusion Thrombophlebitis, phlebothrombosis, and phlegmasia cerulea dolens may all be associated with various degrees of arterial spasm To appreciate the ischemia which arterial spasm can achieve, one needs but to perform an operation upon the superficial femoral vein (as in the days when superficial femoral veins were almost routinely ligated in any patient suspected of having phlebothrombosis of the lower extremity or pulmonary embolism) to observe the marked spasm of the artery which may occur following manipulation in separating the vein from the artery prior to ligation of the vein Virtually no blood is passing through the artery when it is in severe spasm, and certainly no pulse is palpable On the other hand, the injection of local anesthesia around the artery for a distance frequently results in dilatation of this vessel and a return of pulsations In trauma, arterial spasm may be of such severity as to threaten gangrene

While an arteriogram should be performed where required, it is really not essential for determining the level of occlusion, since this will usually be just distal to the point at which normal pulsations can be palpated The coldness of the skin begins several inches below the level of occlusion If one femoral pulse is absent but the opposite one is present, the occlusion will usually be found at the iliac bifurcation on the involved side, if both femorals are absent, the occlusion is at the aortic bifurcation, and so on The level at which the skin temperature changes is best determined by passing the hand fairly rapidly down the skin of the leg Occlusion of the popliteal artery results in a change in skin temperature just above the ankle, occlusion of the bifurcation of the

femoral results in a change in temperature at the junction of the lower and middle thirds of the thigh; occlusion of the common iliac artery may result in a change in skin temperature at the junction of the middle and upper thirds of the thigh (Fig 168) The line of *gangrenous demarcation* will appear several inches below the level of temperature change. It is always desirable, if amputation must be done, to allow sufficient time to make certain of the line of demarcation, so that an adequate amputation can be done initially without the necessity for secondary procedures, except where infection may be present at the time of the first operation That the mortality rate is increased where secondary operations are required has been repeatedly demonstrated and patients who have arterial occlusion are usually poor operative risks to begin with

Unquestionably arterial spasm contributes considerably to the symptomatology of acute arterial occlusion, *in addition to the* actual organic or mechanical obstruction of the arterial lumen but important time can be lost in treating arterial spasm with paravertebral sympathetic blocks in lieu of definitive surgery to re-establish arterial patency

Conservative measures for acute embolic occlusion save few extremities that would not have survived in any event Paravertebral sympathetic block or "continuous caudal anesthesia is probably the most valuable single conservative measure In addition the part is left at room temperature arterial vasodilators are employed, and, where indicated anticoagulants are given

In a review of 330 instances of peripheral arterial embolism Haimovici[71] found that 38 per cent occurred in the femoral arteries, 14 per cent in the popliteal artery, 14 per cent in the common iliac artery 9 per cent at the bifurcation of the aorta 9 per cent in the brachial arteries, and the remainder in miscellaneous portions of the arterial tree Six hours is usually considered the interval following acute occlusion during which *successful embolectomy can be anticipated*, but occasional successes have been reported after much longer intervals Retrograde evacuation of clot is helpful

Arterial Aneurysms

An aneurysm is an abnormal dilatation of an artery that is permanent (Fig. 169) It is caused by some agent process, or predisposition which produces or allows weakening of a portion of the arterial wall with resulting bulging at that point. Among the many agents which may produce injury to the arterial wall, the more important ones are syphilis, arteriosclerosis, certain types of infection and gunshot injuries which may or may not actually pierce the wall of the vessel One other type of interesting aneurysm is the so-called post stenotic' dilatation of an artery which occurs distal to a constriction of the vessel For example, it has been noted that the subclavian may show aneurysm formation distal to compression as in cervical rib or scalenus anticus syndrome The pulmonary artery may show *marked dilatation distal to the stenotic* valve in pulmonic stenosis. Holman[81] reviewed the experimental work, including his own studies, and concluded that post-stenotic dilatation is due to the lateral waves of pressure produced by the jet effect of the stream passing through the narrowed portion of the artery and causing physical disturbances in the movement of the blood stream just distal to the point of constriction (Fig. 170) The particularly important contribution of his report was that it explained the mechanism of a common structural defect in terms of well established principles of physics Once the arterial wall is diseased and begins to dilate from the normal pressure of blood flow, the vessel lumen at the proximal end of the aneurysmal dilatation becomes a relatively constricted point, and so the turbulence effect described by Holman may be a further contributing factor in most aneurysms

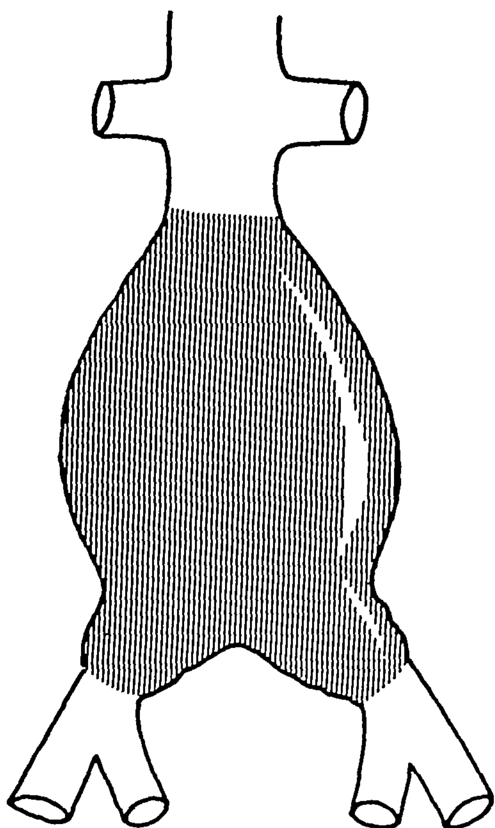
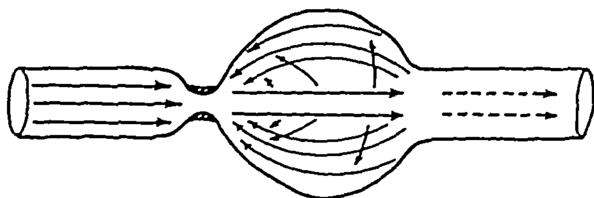




Fig 169 Case study, ruptured abdominal aneurysm S S, a 56-year-old man was suddenly seized with severe left lower abdominal pain when he jumped backward to avoid the kick of a cow Soon thereafter the pain radiated downward into the left testicle, and when admitted to the hospital in shock he was assigned to the urology service with the provisional diagnosis of renal disease Despite occasional episodes of hypotension and a low hematocrit level, the diagnosis of a ruptured abdominal aneurysm was not seriously considered until, after 5 days, a pulsating abdominal mass was detected The aneurysm suddenly began to bleed again, and emergency resection and grafting were performed Postoperatively he almost died of uremia (see Fig 23), but he eventually returned to work Rupture of an aneurysm is not necessarily fatal immediately, and many patients can be saved by prompt surgery

PRESSURE WAVES DISTAL TO STENOSIS



(AFTER HOLMAN)

Fig 170 The lateral pressure waves set up by the jet of fluid past a constriction produce increased stress on the wall of this segment of the vessel Eventually structural defects permit aneurysm formation

In general, aneurysms of the thoracic aorta are often due to syphilis, whereas aneurysms of the abdominal aorta are usually due to arteriosclerosis Formerly it was the thoracic aneurysm that was more frequently encountered, due to the increased incidence of active syphilis throughout the population, but now the abdominal aneurysm is more frequently encountered because of the diminishing incidence of late untreated syphilis and the increasing age of the general population This is a fortunate circumstance, in its way, for it is usually a relatively simple matter to resect and to re-

place with a graft an arteriosclerotic aneurysm of the abdominal aorta, which commonly arises below the renal arteries. It is not as simple a matter to excise the syphilitic aneurysm of the thoracic aorta, which may involve a considerable length of the vessel Yet, aneurysms of virtually all segments of the aorta have now been successfully resected.

The so-called *mycotic aneurysm* is due to involvement of the vessel wall by an infectious process often by a fungus or by embolism from subacute bacterial endocarditis. In this circumstance, as in all others, the arterial wall is weakened at one point and constant pressure within the vessel gradually causes a dilatation of the vessel at this point. Still another type of aneurysm is the so-called *false aneurysm* (pulsating hematoma) which actually represents a hematoma which communicates with the arterial stream through an opening in the vessel wall This is not truly an aneurysm, since here the 'aneurysm" actually consists of a sac of clot, the covering of the sac being a fibrous membrane which has been thrown around the expanding hematoma, that is, continuity of the vessel wall has been lost, as would be the case with a true aneurysm only if it had ruptured (Fig. 173)

A *congenital defect* in the wall of an artery may also be the cause of an aneurysm, particularly of those occurring within the brain, which are of particular interest to neurosurgeons. For example the congenital aneurysm of the internal carotid artery and portions of the circle of Willis is well known Aneurysms may develop in these vessels at any time throughout life, and rupture of these lesions is a major cause of brain hemorrhage They are presently treated either by direct attack or more conservatively by ligation of the common carotid artery on that side.

In general, aneurysms involving the aorta to which most of the subsequent discussion will be directed, are of either the *saccular* or the *fusiform* type The saccular portion involves only one side of the artery and has a 'neck.' By placing a clamp across the neck, one can excise the aneurysm without stopping the flow of blood through the aorta and can then suture the defect in the wall of the aorta This procedure has been termed "lateral aortorrhaphy"

Aneurysms with at least some fusiform component are, in our clinic, far more common, and they require the actual excision of a portion of the aorta and replacement with a homograft or some plastic material For example, in the case of syphilitic aneurysms of the ascending aorta and arch the involvement may begin as a diffuse enlargement of the entire ascending aorta and a portion of the arch. Thus it may be difficult or impossible to find a point on the aorta where the diameter is relatively small and where one can state that here is relatively normal aorta, to which the graft may be sutured. The requirement of continuing blood flow during the process of inserting the thoracic graft originally necessitated the use of some type of bypass by means of plastic tubes or other material Later DeBakey, Cooley, and Creech used the pump-oxygenator successfully for this purpose The heart will fail in a matter of minutes if the ascending aorta is cross clamped without providing for emptying the heart of blood by some form of bypass or by placing the heart at rest by the use of the pump-oxygenator with inflow occlusion

Whereas one cannot cross clamp the thoracic aorta for more than a relatively few minutes (this being increased to almost an hour by the use of hypothermia) the abdominal aorta below the renal vessels can be clamped off for much more than an hour in the normothermic individual without serious consequences. Therefore, in addition to the fact that control of the aortic blood flow is more readily accomplished in the lower abdominal aorta, the surgeon may also proceed with the firm knowledge that the occlusion and division of the aorta for whatever reasonable amount of time is required to



Fig 171 Dissecting aneurysm of aorta (see case J D in text) *Upper left* Probe in site of origin of dissecting aneurysm Note true aneurysm just above *Lower left* Intramural clot below renal arteries *Right* The entire descending aorta was involved

achieve satisfactory insertion of the graft will not often result in serious consequences to the patient—such as incontinence, renal failure, or gangrene of the extremity Nevertheless, this is not to say that the occlusion time should not be minimized by careful planning as the operation proceeds

DISSECTING ANEURYSM The dissecting aneurysm is not really an aneurysm in the usual sense in which the word is used In effect, the blood stream finds an opening between the layers of the aortic wall, and the pressure of the stream then forces the layers of the wall apart While cystic necrosis of the media, or syphilis, is the cause in many cases, in the ones that we have observed the dissection has appeared to be precipitated by an atheromatous plaque (Fig 171) Many of these patients have hypertension The process usually begins in the aortic arch or in the ascending aorta and progresses downward through the media The following case presents certain features of this condition and emphasizes the difficulty in achieving an accurate diagnosis in some patients

Case study J D, a 48-year-old man was awakened at night with abdominal pain which became progressively more severe His local physician had seen him and, because of a mass in the abdomen and other symptoms, had diagnosed a ruptured abdominal aneurysm It was known that arterial hypertension and a positive serology had been present previously

On admission to the University Hospital

he was obviously critically ill and was complaining of severe abdominal pain with pain down the right leg. The pulse was rapid but the blood pressure level was one of mild hypertension. The abdomen was tense and there was a palpable mass in the epigastrium which actually enlarged to some extent while the patient was lying on the x ray table awaiting an aortogram. Because of his critical condition, the radiologist elected to perform the aortogram in a retrograde fashion, by passing a polyethylene catheter up the femoral artery This resulted twice in most peculiar findings. It appeared to show no renal visualization on one side but renal visualization on the other side, and the possibility of a dissecting aneurysm was seriously considered from the bizarre findings on the aortogram By this time however, the patient was complaining of increasingly severe pain in the abdomen, and the mass in the abdomen was visibly enlarging Accordingly while the possibility of a dissecting aneurysm beginning in the thoracic aorta was still seriously entertained, it was considered imperative to open the abdomen and control what was almost certain to be an expanding hematoma As soon as the peritoneal cavity was entered a retroperitoneal hematoma was noted to lie in the general region of the pancreas and the celiac axis. After placing tapes around the aorta above and below, a direct attack was made upon the apparent source of the hemorrhage. This proved to be posterior to the pancreas and, with appropriate dissection, it was eventually found to arise from a branch of the celiac axis. Still further dissection revealed that the hemorrhage was arising from the wall of the splenic artery about 2 inches distal to its origin. As the wall of the artery was cut across after ligation it was seen that a dissecting aneurysm had separated the media from the adventitia and that the latter had ruptured to produce the retroperitoneal hemorrhage There was a strong thrill in the gastrohepatic artery but its pulsation was excellent—as was the pulsation in each renal artery and in all other major branches of the abdominal aorta, including the iliac vessels The aorta itself felt normal

At this point a major decision had to be made On the basis of probabilities, it seemed likely that the dissecting aneurysm involving the splenic artery was one that had begun in the thoracic aorta and extended downward. On the other hand, at no time had the patient had pain in his chest and all pulses of the arms, neck, and legs were of good volume, save for the right femoral pulse which was definitely diminished Nevertheless, the right iliac pulse was good Therefore, because of the patient's poor condition and the fact that the source of the bleeding had now been controlled—in addition to the fact that it was considered possible that the dissection might be a local phenomenon without a thoracic component (again, the aorta was normal to palpation) —it was elected to close the abdomen and not to enter the chest for the purpose of dealing with a possible dissecting aneurysm involving the thoracic aorta.

Postoperatively the patient did well from the general standpoint of maintenance of blood pressure and other functions, though he formed virtually no urine during the 24 hours that he lived. On the day following operation it was apparent that he was doing poorly, though the blood pressure was well maintained until a few hours preceding death The pain in the right leg had increased but otherwise symptoms were not remarkable. He died in shock approximately 24 hours following the operation, from no clearly discernible cause

Autopsy revealed a dissecting aneurysm which had begun just proximal to a large atheromatous plaque at the junction of the arch and the descending aorta (Fig 171) Approximately one half of the circumference of the aorta was involved by the process. There was a true aneurysm of the distal aortic arch just proximal to the point of dissection, and there were extensive syphilitic changes in the thoracic aorta. The cause of death was not readily apparent since there had been no further bleeding. Ischemia

of the spinal cord could have been an etiologic factor in the shock present terminally, certainly the failure to excrete urine for 24 hours was not of sufficient significance to cause death due to renal failure, in the absence of potassium intoxication Hepatic blood flow had apparently not been occluded

In summary, a dissecting aneurysm is an exceedingly serious condition which usually ends in death, and immediate death occurs in approximately one-third of the cases More than 50 per cent die within the first 24 hours of the onset of symptoms and only a few live for more than a month Nevertheless, various groups have operated upon these lesions and have achieved some encouraging results



Fig 172 Ruptured abdominal aneurysm resected with homografting This patient died of renal failure

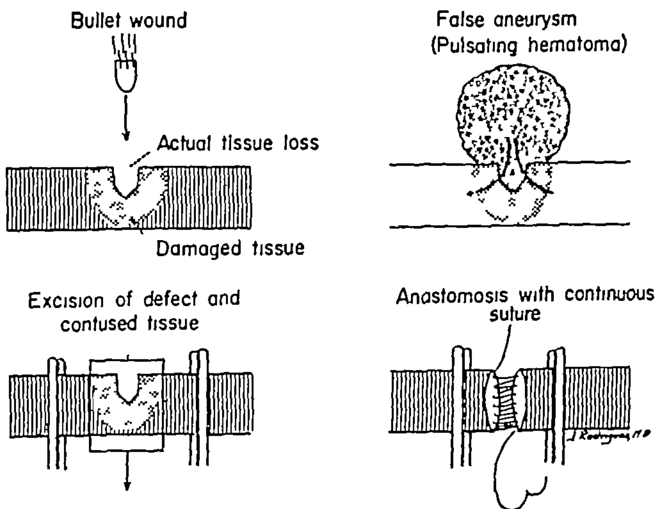


Fig 173 Gunshot injuries produce not only actual tissue loss but also radiating damage to the surrounding arterial wall This damaged tissue should also be excised Occasionally, especially following bird-shot injury, the arterial lumen will have been occluded by intramural hemorrhage when no defect or bleeding is visible on direct inspection of the vessel We prefer to excise the damaged segment of the artery and to perform end-to-end anastomosis Such primary arterial anastomoses following injury are almost uniformly successful

PROGNOSIS IN ANEURYSMS The prognosis of any particular aneurysm depends upon its location, and this may be determined by angiography It has been estimated that the average length of life in untreated abdominal aneurysms is from 6 to 12 months following diagnosis of the lesion While homografts may themselves become aneurysmal, there can be little question that the outlook for patients with aortic aneurysms, especially abdominal aneurysms, has been greatly improved by excisional surgery Again, from the technical standpoint it is much simpler to excise and graft an aneurysm in the abdomen arising below the renal arteries than it is to excise a lesion in the upper abdomen or chest Rupture of an abdominal aneurysm (Fig 172) is not necessarily fatal if operated upon promptly (Fig 169) With the use of temporary bypasses almost any segment of the aorta can be operated upon It is too early to state what the longterm results of excisional aortic surgery will be

Traumatic Arterial Injuries (Fig. 173)

The problems associated with acute arterial injury, whether due to gunshot wounds or to stabbing, fall roughly into the following categories (1) acute severance of the vessel, with impending ischemic gangrene if blood flow is not successfully re-established, (2) more subacute disease, with the formation of a false aneurysm (pulsating hematoma), and (3) chronic disease with arteriovenous fistula In addition, (4) it has been mentioned that actual arterial wall dissolution may not have been present but that injury to neighboring structures or perhaps even the outer portion of the arterial wall by a bullet may result in the syndrome of

causalgia[128] This complex consists of sweating, paresthesias, and other phenomena which may be relieved by sympathectomy on the involved side It can become chronic and quite disabling

ACUTE ARTERIAL INJURY WITH LOSS OF VESSEL INTEGRITY The frequency with which *gunshot injuries* are admitted to civilian hospitals in different parts of the United States and, indeed, to different hospitals within the same city, varies markedly In those hospitals in which the members of the house staff rarely see an acute gunshot injury or a serious stab wound an important phase of surgical training is neglected Vascular injuries are frequently of the most urgent nature but they are often relatively easily managed once their fundamental nature is clearly understood

The following case study is illustrative of many of the problems which accompany the severance of a major artery by a bullet or knife.

Case study The patient was a 23 year-old man who had been shot in a gun fight while intoxicated He was brought to the University Hospital in a state of shock, having lost an undetermined volume of blood from a wound in the lower portion of the right thigh. It was not possible of course to know how much blood he had lost, but the fact that he was in shock in the reclining position had he not also been intoxicated would have indicated that he had lost a liter or more of blood Hypotension responds less readily to a given volume of transfusion in the inebriated subject perhaps because of both capillary vasodilatation and less efficient arteriolar vasoconstrictor response to the oligemic state.

Physical examination had already demonstrated that whereas the left foot was warm and had a good dorsalis pedis pulse (after a relatively normal blood pressure had been restored by blood transfusion) the right foot was cold and no pulses were palpable either over the popliteal area or below rendering arterial damage highly likely There was no major neurologic deficit.

At operation, begun with a pneumatic tourniquet placed about the upper right thigh but not inflated, the hematoma was evacuated and the path of the bullet exposed. The sciatic nerve was intact, as had been expected from the neurologic examination prior to operation, but it was found that the popliteal artery had been almost completely severed, being lacerated into shreds for a distance of approximately 1 inch. This had of course prevented retraction of the two ends and had resulted in greater blood loss than would have occurred otherwise. (In a similar case in which the wound had been inflicted with a butcher knife, the ends of the severed femoral artery had retracted and bleeding had ceased entirely, the patient being in relatively mild shock on admission prior to successful end-to-end anastomosis.) Bleeding from the artery was brisk as soon as the hematoma was removed and it was necessary to inflate the pneumatic tourniquet to control blood loss until the artery had been freed up and controlled both above and below the site of injury

After thorough debridement of the surrounding musculature the ends of the popliteal artery were freshened for a distance of perhaps 0 5 cm, since the blast of the bullet injury had probably caused arterial wall damage for some distance adjacent to the point of actual division of the vessel To our dismay it was now impossible to bring the ends of the artery together for anastomosis, and no suitable graft for an artery of this small caliber was available at that time A venous graft was considered but not used when it was found possible, by sharply flexing the lower leg on the thigh, to bring the ends of the artery together The dorsalis pedis pulse was promptly restored by the anastomosis, and it remained good after operation A plaster cast was applied and then bivalved to keep the knee flexed for 1 week. At the end of this time the leg was removed from the cast and gradual exercises were prescribed in order to straighten the knee extension was complete in 2 weeks. Foot

pulses remained strong, and the patient had a completely successful result

Comment Had the ends of the popliteal artery in this case been ligated instead of anastomosed, the chances of losing the foot would have been greater than 50 per cent Ligation of major arteries without attempted anastomosis is rapidly becoming a thing of the past With reasonable care the flow can be restored in the vast majority of instances where little arterial length has been lost

As for technical requirements, the following are helpful but none are indispensable pneumatic tourniquet, 0000 and 00000 arterial silk, a light weight needle holder or a straight hemostat, fine forceps, heavy bulldog clamps, and various types of arterial clamps When the patient is inebriated a general anesthetic is employed, and adequate amounts of blood for transfusion are essential Almost any type of stitch that is hemostatic will suffice, though we prefer either a continuous running "baseball" suture or the interrupted everting mattress stitch

Arterial injuries are often associated with *nerve injuries*, and it must remain a matter of judgment as to whether a severed nerve is to be sutured at the time of the original operation or whether the wound will be closed and the nerve sutured at the end of 3 months Immediate suture is often advisable If not, the ends of the nerve should be tagged so that they will be readily identifiable if it is decided to delay nerve repair This is often done with metal clips, but it is probably more practically done with black silk ligatures that can be readily identified and traced at the subsequent operation

FALSE ANEURYSM OR PULSATING HEMATOMA

If the artery involved is not one of such significance that failure to restore continuity will result in gangrene of the extremity, or if the injury has not actually severed the artery but has made a defect in its wall, the involved extremity may survive the episode However, a chronic leakage of blood from the hole in the wall of the vessel may result in a so-called *false aneurysm* or *pulsating hematoma* This may gradually increase in size due both to the escape of further blood from the defect in the wall of the artery into surrounding tissues and to the fact that fluid is drawn into the clot, such as occurs in a subdural hematoma The picture is particularly confusing when the pulses distal to the point of injury are still present, if weak The term false aneurysm, as mentioned above, is derived from the fact that a fibrinous membrane tends to form around the hematoma, which does pulsate because it communicates with the arterial lumen From time to time episodes of further hemorrhage tend to occur, and failure to diagnose correctly and to treat definitively results in much unnecessarily prolonged morbidity In fact, of all the conditions which may be associated with arterial injury, the pulsating hematoma is the one which, in our experience, most often proves confusing to personnel in training The reasons for this are several First, the obvious immediacy of acute trauma leads any person with even meager experience to suspect the possibility of arterial injury, especially if considerable blood has been lost and the extremity is cold and pulseless On the other hand, the pulsating hematoma may not be apparent at the time of admission, due to the fact that whereas considerable blood may have been lost, clotting has now occurred Or, the hematoma lies deep within the musculature and a swelling of the thigh, for example, may be attributed to edema following the injury rather than to blood which has escaped into the muscle planes Another patient may give the history of fluctuations in the size of the extremity Still another may have sustained a stab wound without apparent serious consequences at the time, only to develop weeks later a swelling which may actually be drained surgically by the untrained person, for at times the false aneurysm simulates a collection of pus This can be, of course, an informative experience, since the physician is usually not prepared with blood for transfusion or with a carefully placed pneumatic cuff with which to control hemorrhage The following case will illus-

trate the delay which may precede an accurate diagnosis, even on a surgical service where such injuries are relatively common

Case study The patient was a 28-year-old woman who had been stabbed in the upper left thigh Although a considerable amount of blood had been lost, she was not in serious shock at the time of admission. Blood was oozing from the knife wound of the left thigh, and on exploration it was found that several muscle bundles had been severed, apparently the source of the oozing. The femoral and sciatic nerves were intact, as determined preoperatively by careful neurologic examination and, in the case of the femoral nerve at operation. The femoral artery was thought not to be involved since all leg pulses were good, and it was not formally exposed. The thigh was drained through and through

Following operation the patient did well for several days but there then developed much swelling of the thigh which appeared to increase the circumference fairly evenly At first the swelling was judged to be due to edema, but when later she developed fever opinion veered toward an infection and a possible collection of purulent material. Accordingly, the residents on night duty were assigned to reopen the wound and to examine for pus This was done, unfortunately by the most junior person, the procedure being considered a most simple one. He found some old blood, but he did not actually explore deeply enough to come upon the major collection of what was actually a hematoma of large proportions To be brief, the patient was subsequently again explored but again the significance of the deep hematoma that was found was not entirely appreciated though a considerable portion of the old clot was removed There was still no interference with the palpable arterial supply of the extremity Finally after a period of several weeks the swelling had largely subsided and it was felt that at last the patient could be allowed to go home. However just as she was dressing to leave the hospital blood began to emerge briskly from the depths of the almost healed wound and she had to be taken immediately to the operating room and a pneumatic tourniquet applied just distal to the inguinal crease This time the wound was thoroughly explored by an experienced person who found a hole in the wall of the profunda femoris artery (Fig 166) Since this artery could readily be sacrificed, it was ligated both proximally and distally and then divided, and the patient was discharged from the hospital in 5 days—the time she should have stayed following the original injury, instead of the actual 6 weeks. It is not enough to reduce mortality—morbidity has also to be considered

ARTERIOVENOUS (A V) FISTULA. This is the condition which exists when blood passes directly from an artery to a vein (Fig. 174) without first flowing through the intervening capillaries. The defect between the two vessels may be traumatic, congenital or infectious in origin, or even normal.

Trauma is an especially prominent cause of arteriovenous fistulas Congenital lesions are also frequent, such as the so called "cavernous hemangioma" of an extremity, this may extend well up on the lower abdomen and buttock. The pulmonary arteriovenous fistula[133] permits the unoxygenated venous blood in a pulmonary artery to flow directly into a pulmonary vein without first being oxygenated producing cyanosis and perhaps clubbing of fingers and toes

The *traumatic arteriovenous fistula* usually follows a knife wound or a gunshot injury though it may not be apparent until days weeks, or even months later The abnormal communication can occur anywhere in the body that an artery and a vein lie in close proximity to each other The *signs and symptoms* of arteriovenous fistula were described accurately by William Hunter as early as 1757 He noted that the thrill and bruit could both be stopped by pressure over the proximal portion of the artery or at the site of the fistula[3] As soon as the communication has been established between the artery and the vein, whether this occurs im

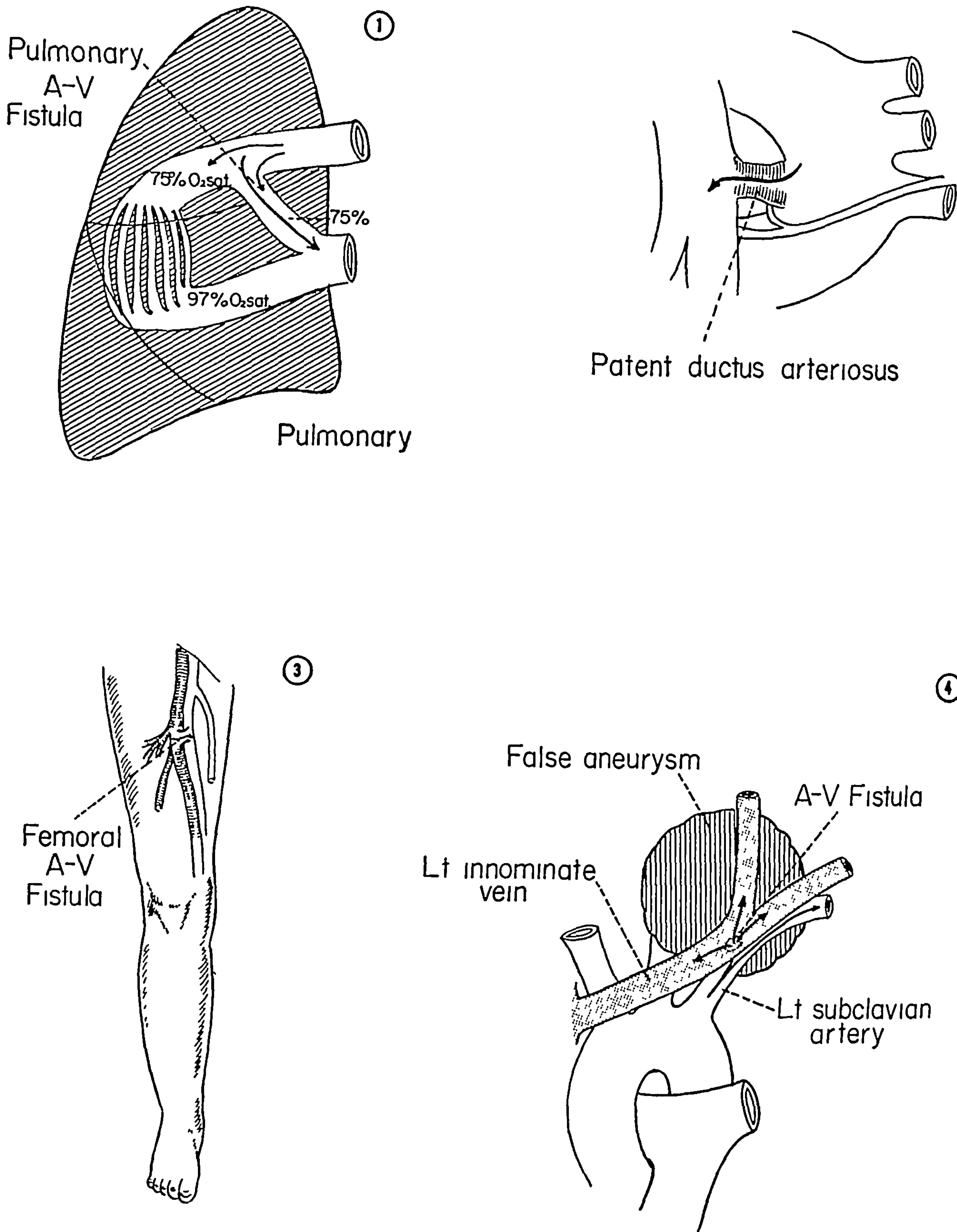


Fig 174 Representative arteriovenous (A-V) fistulas Direct arteriovenous communications (without intervening capillaries) may occur anywhere in the body—between elements of the systemic circulation, between elements of the pulmonary circulation, or between the systemic and the pulmonary circulations (patent ductus) All impose an increased workload upon the heart and, if large enough, can produce cardiac decompensation

mediately or after the lapse of variable amounts of time, there is likely to be some swelling of the involved extremity, especially distal to the site of the communication The veins of the involved part are commonly dilated by the unaccustomed arterial blood pressure, and their walls are thickened ("arterialization") The skin temperature of that

leg is increased due to the increased rate of blood flow, particularly adjacent to the fistula. The increase in collateral circulation may be relatively enormous, and the arterial oxygen saturation in communicating veins is abnormally high. A thrill is palpable and a bruit can usually be heard on auscultation, both typically being present throughout the cardiac cycle. If the communication is large the blood flow to the more distal part of the involved extremity can be diminished to the extent that gangrene may occur, that is, the flow to the foot is short circuited. The precise location of the communication can be demonstrated with angiography. Classically occlusion of the fistulous opening by firm point pressure produces a slowing of the pulse rate, a rise in diastolic pressure and a fall in systolic blood pressure, plus a reduction in the distention of the adjacent veins.

The *prognosis* in arteriovenous fistula is determined primarily by the size of the opening and its proximity to the heart. The resulting relative ischemia of the extremity distal to the fistula may or may not be so great as to produce gangrene. However, the changes that are most threatening to life are the cardiac derangements which occur. The increased workload imposed upon the heart by the fistula may eventuate in cardiac decompensation, with or without an increase in blood volume. Moreover, arteriovenous fistulas have long been known to be associated with subacute bacterial endocarditis. In 1935, Hamman and Rienhoff[78] reported a case of *Streptococcus viridans* septicemia cured by excision of a fistula between the iliac artery and vein, and in 1946 Cutler and Wolf[40] reported an acquired arteriovenous fistula with coexistent subacute bacterial endocarditis and endarteritis. Moreover, prior to the advent of antibiotics an occasional case of subacute bacterial endocarditis was cured by the closure of an associated patent ductus arteriosus also an arteriovenous fistula. Later Lillehei and his associates[104] demonstrated that subacute bacterial endocarditis could be produced experimentally in dogs by constructing large bilateral iliac arteriovenous fistulas.

In brief, cardiac decompensation is by far the most common serious complication of arteriovenous fistulas. If the fistula is successfully closed early enough, the enlarged heart may return to normal size and the usual circulatory stability may be restored (Fig. 175).

The management of arteriovenous fistula has undergone certain modifications in recent years. Whereas it was formerly the practice to allow at least 6 weeks for the development of collateral circulation subsequent to the diagnosis of an arteriovenous fistula, if the fistula had not persisted for weeks already, the present tendency is to operate upon these defects promptly, with a view to restoring end to-end continuity of the artery. That is, the objective of quadruple ligation, consisting of excision of the segment of both artery and vein involved in the fistula, with consequent loss of arterial continuity, is being replaced by the objective of restoring end to-end continuity of the vessel either by excision of the defect with end to end anastomosis of the artery or by the insertion of a homograft—especially in the acute case. For even though fully developed collateral circulation may prevent gangrene following ligation of the involved artery intermittent claudication may be present postoperatively if arterial continuity cannot be restored.

Nevertheless, many still prefer to allow time for a collateral circulation to develop, provided the arterial defect is not discovered immediately after injury, at which time it can readily be exposed and repaired. The reason for allowing time in the more chronic fistula is that the inflammatory process which surrounds the fistula leads to a fibrosis which renders planes of cleavage difficult to develop, and it may be all but impossible to free the artery in such a way as to offer an opportunity for excision of the arterial defect with end to-end anastomosis. Despite the fact that this may be the objective of the operator, it frequently happens one way or another, that a quadruple



Fig 175 Case study This 34-year-old patient was stabbed in the neck almost 14 years before hospitalization Many months following injury a "buzzing" began in the neck over a mass that gradually enlarged During a second post-injury pregnancy she was in heart failure from what doctors told her was an arteriovenous fistula She was forced by the heart failure to agree to surgery At operation the cervical mass consisted chiefly of an huge aneurysmal dilatation of the left innominate and internal jugular veins There was a false aneurysm (Fig 174-4) eroding into the cervical spine, in conjunction with a large (almost 1.5 cm) fistula between the left innominate vein and the left subclavian artery

ligation is finally performed If this is done, it is important that sufficient time has elapsed to permit adequate collateral circulation to develop Of course, an arterial graft should be available and should be used where possible

As with all arterial surgery, the major entering vessels should be secured both proximal and distal to the fistula before a direct attack is made upon the fistula itself, for the artery is far more readily exposed through noninflamed tissues Here too a pneumatic tourniquet, if feasible, may prove most helpful at times Sharp dissection is preferred, and important nerves are obviously to be preserved If the arterial anastomosis is successful there will usually be an immediate pulsation in the dorsalis pedis and posterior tibial arteries at the close of the anastomosis If this does not occur, sympathetic block should be employed However, in our experience infiltration

round the artery for a considerable distance with 2 per cent procaine usually overcomes arterial spasm to the extent that at least some pulsation can be palpated distally, hough this may increase as vasospasm diminishes. In some patients the maximum pulsations may not be realized until several days following an anastomosis The thrill and bruit will of course disappear following successful management of the fistula

CAUSALGIA FURTHER COMMENT One of the most disabling types of pain which may follow traumatic neurovascular injury is that termed causalgia.[128] It may result from exposure to cold, gunshot wounds, or less conspicuous circumstances. For example, a sergeant fell while carrying a case of beer to the Officers' Club, and there followed prolonged pain, burning, and excessive sweating in the right shoulder and arm, associated later with muscle atrophy and marked disability No major nerve deficits could be identified and the radial pulse was good The symptomatology resembled that often characterized as Sudek s atrophy or dystrophy, and was similar also to the pain and atrophy of the intrinsic hand muscles secondary to coronary occlusion (shoulder hand syndrome)

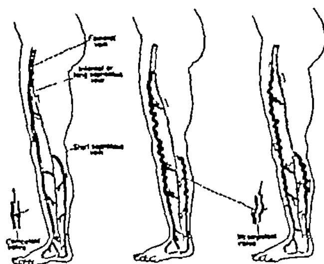
Causalgia is often associated with an extreme cutaneous hyperalgesia which gradually is replaced by trophic changes consisting of scaling discoloration and a shiny appearance suggestive of that due to chronic ischemia.

The mechanism of causalgia is poorly understood but characteristically the pain is relieved by paravertebral sympathetic block or sympathectomy—emphasizing the importance of the sympathetic nervous elements in the genesis of the condition.

Volkmann s ischemic contracture is due in part to brachial artery compression but also to spasm of this vessel which, if not relieved may cause gangrene.

Disease of the Veins (Figs 166 and 176)

Fewer precise physiologic data are available regarding venous disease than for arterial disease Whereas the arteries usually represent single and main trunks rendering the hemodynamics more readily evaluated, veins are tortuous, multiple, and less readily available for certain hemodynamic and other studies. Similarly, whereas there is a considerable body of accurate pathologic and physiologic information regarding lesions which cause structural changes in the walls of arteries there is a dismaying paucity of dependable information regarding the factors which produce structural



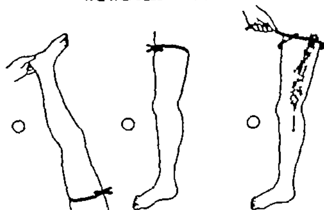


Fig 176 Tests for competency of valves in long saphenous vein (after COLE, W H., AND ELMAN R. *Textbook of General Surgery* Ed. 5 New York D Appleton-Century Company Inc., 1948) *Above* Reversed flow in long saphenous and communicating veins. *Below* (*A*) Tourniquet applied after varices collapsed by elevating leg (*B*) With tourniquet applied long saphenous does not fill, indicating *competent valves in communicating veins* (*C*) Saphenous fills when tourniquet released, proving incompetence of valves of long or great saphenous.

changes in veins to permit the development of so common a condition as varicose veins Nevertheless, knowledge of venous physiology is increasing and some of the more important points will be reviewed

METHODS OF STUDYING VENOUS DISEASE The *history* is of paramount importance in eliciting many of the important findings upon which reliable diagnosis and treatment of venous disease can be based For example, varicose veins, deep venous thrombosis associated with thrombophlebitis, massive venous occlusion, and the migrating phlebitis of thromboangiitis obliterans are all associated with pain or other symptoms which when properly evaluated may suggest the probable diagnosis

On physical examination one should note the presence or absence of the following venous distention, thrombosis and tenderness in superficial veins, or increased circumference of the extremity with edema suggesting deep venous thrombosis An increased skin temperature with venous distention may suggest an arteriovenous fistula, in contrast, edematous swelling with diminished skin temperature may suggest the presence of deep venous thrombosis The clinical tests employed to determine the presence or absence of valvular competency and patency of various portions of the saphenous and deep vein systems are shown in Figure 176 Venograms supplement such tests, as seen below

Measurements of venous pressure may be made A number of investigators have studied the venous pressure in veins of the lower extremity, both at rest and during exercise Pollack and Wood[121] found that venous pressure in the great saphenous vein at the ankle averaged 11 7 mm Hg (range, 7 0 to 21 6) in the recumbent position, 56 0 mm Hg (range, 45 0 to 67 5) in the sitting position, and 86 8 mm Hg (range, 78 5 to 92 6) in the resting standing position They considered that the venous pressure at the ankle in the resting sitting or resting standing position was sufficient to support a column of blood to approximately the level of the third thoracic interspace at the sternum In studying the venous pressure changes produced by a single step, they found that there was an average rise in pressure of 10 mm Hg from the standing control level before the heel was lifted from the floor at the beginning of the step, an average fall of 52 mm Hg (range, 28 0 to 80 5) occurred with the foot off the floor, as the heel touched the floor there was a slight rise in pressure, followed by another fall to the previous low level while the heel settled on the floor and the body weight was redistributed The pressure returned to the control level in a time of 22 9 seconds (range, 11 0 to 37 0) as the subject resumed the quiet standing position

In clinical practice, however, measurements of venous pressures in the lower extremities have no well established rôle in the management of venous disease

Venous angiography is being increasingly utilized as a method of diagnosing obstruction of different veins, particularly those of the lower extremities Berberich and Hirsch[20] are given credit for being the first (1923) to inject radiopaque material into the veins of human beings, and in 1936 Barker and Camp[10] employed venography in the study of obstructive venous lesions More recently, Boyd and associates[30] have described their technic of lower limb phlebography and presented illustrations of some of the venous lesions that may be anticipated The pitfalls encountered in interpreting venograms were emphasized, and these are not inconsiderable The vein may be superimposed upon a limb or bone, and there may be serious question that filling defects are due to organic lesions. Moreover, repeated studies are of value, since a vein that did not fill with contrast medium during the first study might have been in spasm, blocked by an occluding thrombus, locally occluded, or even normal Venospasm, constricting the vein to the point of complete occlusion, can be associated with recent acute thrombophlebitis, which may be suggested clinically However, absent or

poor venous filling in a normal or possibly compressed vein should not be interpreted definitively without a second study The presence of distended collateral veins may assist in the further identification of a point of deep vein occlusion suggested by the venogram. It was noted by Boyd and his coworkers that dilution of the contrast medium is sometimes seen proximal to the site of an arteriovenous fistula, or at the ends of the column of contrast medium, and that this should not be interpreted as a filling defect. Phlebography is definitely valuable in demonstrating obstruction by deep phlebitis, or in examining preoperatively and postoperatively for the effects of saphenous vein surgery or for the presence or absence of deep vein patency before surgery is done for varicose saphenous veins, where doubt exists as to the advisability of removing the superficial venous channels when occlusion of the deep veins may exist. Atrophy of the venous system is occasionally demonstrated in conditions of muscle wasting such as may follow arteriosclerotic obliterative disease. Recanalization of thrombosed or ligated veins may also be demonstrated, and Dow[44] applied venography to the diagnosis and study of the process of recurrence of varicose veins following surgery Though recanalization was demonstrated, the most common cause of recurrence of varicose veins was the failure to ligate at operation all tributaries to the great saphenous vein.

VARICOSE VEINS *Etiology* While varicose veins are among the oldest surgical diseases known and surely one of the most common, comparatively little is proven regarding precise causes or methods of prevention. It has often been stated that varicose veins of the lower extremities represent a price that the human being pays for assuming the upright posture, yet obviously not all persons develop varicose veins. Among contributory factors that are clearly recognized are first, a congenital weakness of the venous walls and valves, which is more prevalent in some families than in others. Second, varices may follow deep venous thrombosis in the extremities and are often seen during pregnancy Indeed, the increased incidence in pregnant women is one of the more obvious effects of back pressure due to the descent of the fetus in the pelvis, though certainly hormonal factors are by no means excluded in this connection, for example, a nurse of our acquaintance stated that the size of the veins of her forearms and hands had increased over the months of her pregnancy (due to increased blood volume?) Third, prolonged standing undoubtedly promotes the formation of varices, or at least aggravates the condition and its sequelae and it has been shown that the pressure in the saphenous vein at the ankle is less in the recumbent position than in the sitting position and less in the sitting position than in the standing position—and especially in the presence of incompetent valves of the veins.

To summarize, the more important factors in the development of varicose veins in normal subjects who are not pregnant would appear to be, first, a familial history of weakness of the venous structures and, second, social circumstances which require prolonged standing. Varicose veins are also frequently associated with obesity, perhaps due to the poor support and compression that fat affords.

Pathophysiology As a result of the dilatation, elongation, loss of elasticity of the vein, and the disappearance or deranged function of the venous valves, a pathologic variation in venous blood flow occurs which affects primarily the great saphenous system. Incompetency of the valves of the long saphenous vein itself may allow an unbroken column of blood to extend all the way from the heart to the ankle, there being no valves in the inferior vena cava and often not even in the iliac and femoral vein central to the entrance of the saphenous vein Moreover, even should valves in the iliac and proximal femoral vein be competent, the column of blood in the saphenous vein itself would still exert considerable hydrostatic pressure at the ankle Consequent

it is at the ankle that the more severe complications or sequelae of varicose veins usually appear

A further contributing factor may be incompetency of the valves of the communicating veins between the saphenous and the deep vein system Normally blood flows from the saphenous to the deep vein rather than in the reverse direction, when valves of the deep vein become incompetent, increased pressure is transmitted to the valves of the communicating veins These valves may in turn be rendered incompetent, so that blood flows to the saphenous vein from the popliteal or femoral vein, instead of in the opposite direction as normally Muscular action is less effective in compressing and emptying the saphenous vein than the deep veins, and the increased pressure is poorly tolerated by the tissues at the angle In 1939 McPheeters and Anderson[110] demonstrated with radiopaque substances a retrograde flow from the upper saphenous vein to the lower saphenous and thence to the deep venous channel below and, occasionally, back from the upper veins of the thigh, where incompetent valves were present in the deep vein, to the saphenous vein again Other studies have demonstrated that while in normal subjects the radiopaque material injected at the ankle may be seen only in the more direct channels to the heart, in the presence of saphenous varices it remains in the numerous dilated tortuous collateral veins for a considerable period of time before gradually being cleared from these vessels

The venous stasis, with concurrent derangements in tissue metabolism, results in a characteristic train of visible changes Chronic edema of the ankle is followed by an induration of the skin and subcutaneous tissues, with or without hyperpigmentation of the overlying skin These changes most often appear just above the medial malleolus, above the underlying long saphenous vein The induration and inflammation may represent, in fact, a chronic low grade cellulitis, though specific microorganisms are not commonly cultured from subcutaneous biopsy specimens The brawny induration and brownish discoloration may persist for many months before actual ulceration occurs and, if corrective surgery is performed during this period, a gratifying regression of these changes of the lower leg may be observed in subsequent weeks and months We have in mind the case of a rather obese elderly lady who had well developed induration and some pigmentation of the entire thickness of a large area of the skin above the medial malleolus Ligation of the great saphenous vein and its branches, with stripping of this system down to the ankle beneath the area of induration—and the subsequent use of supportive elastic stockings up to the knee—resulted in a gradual softening of the induration which, had it persisted, would very likely have eventually resulted in the familiar "varicose ulcer" The degree of pigmentation also lessened over the months, and eventually the elastic stockings were discarded

Once *ulceration* has occurred, however, treatment is not nearly so satisfactory This is due both to the fact that the pathologic condition of underlying tissue was allowed to reach a degree that permitted ulceration to occur, and to the fact that it is difficult to restore normal, full thickness skin over the ulcer site after it is excised According to Summers,[147] varicose ulcers have been recognized from the time of Hippocrates Ulceration, with its attendant infection and pain, results in considerable disability, a factor of the greatest concern where the individual is the breadwinner of the family and must be on his feet much of the time Yet, one man we examined had done manual labor despite the presence of a large varicose ulcer for more than 50 years

Diagnosis of varicose veins Symptomatology —Varicose veins usually develop over a period of years, but since the dilated veins themselves are not often incapacitating, the patient may neglect to seek treatment until the condition is far advanced Moreover, prior to the development of cell-

ulitis and ulceration at the ankle there may be no symptoms, though one which is fairly frequent is a "dragging" or painful sensation in the distended varices This is much more annoying to some individuals than to others Superficial thromboses may occur at times surrounded by inflammatory changes. Another complication is that a vein immediately beneath the atrophic skin may rupture through and be the source of annoying hemorrhage, though bleeding is even more likely to occur from the bed of an ulcer The bleeding through a minute skin defect may prove a rather pesky problem to manage in the emergency room It may be best to incise the skin under local anesthesia and formally to expose a segment of the bleeding vein This is then ligated with chromic catgut, since silk might act as a foreign body in the presence of infection and perhaps result in a draining sinus Bleeding from an ulcer bed can usually be controlled with pressure

Other symptoms of varicose veins that are occasionally encountered are itching, paresthesias, burning, and muscular cramps The eczematoid dermatitis of the lower extremity usually associated with underlying edema and induration which may eventually result in ulceration, has been referred to above. Abnormal fatigability of the leg is noted by some patients, though this is not always well correlated with the severity of the varices.

Physical Examination —The physical examination need not be dwelt upon here but the objective is to evaluate the extent of valvular incompetence the location and extent of the venous dilatation, and the progression or lack of progression of the changes in the skin of the lower leg which may suggest impending ulceration By means of both the history and physical examination one attempts to exclude the probability of complicating conditions such as thromboangitis obliterans, deep venous phlebitis and thrombosis arteriovenous fistula and other diseases

Having established the diagnosis of varicose veins due probably to incompetent valves, the next step is to determine whether or not the valves of the long saphenous vein are incompetent and the level of this incompetence The presence and the level of incompetent communicating veins between the saphenous vein and the deep veins should be established, and the status of the short saphenous vein which courses up the posterior surface of the calf and enters the popliteal vein recorded Finally, the patency and the competency of the valves of the deep veins of the leg must also be assessed For to strip the long saphenous vein and to ligate the short saphenous vein in the absence of patent deep veins can result in a very serious circulatory disturbance due to obstruction of venous return from the leg, as the writer once had occasion to observe The patient developed much swelling of the leg with blister formation, and for a time the actual viability of the extremity was in doubt. Prolonged disability resulted, and the man was not able to walk normally for months Late venograms demonstrated obstruction of the deep veins of the leg which had doubtless been present before the long saphenous vein was stripped.

The usual tests for valvular competency of leg veins are shown in Figure 176

Treatment of varicose veins. In the over-all view, once incompetency of the valves of a long saphenous vein has resulted in significant varices, prophylactic high ligation with stripping is the procedure of choice, provided that the deep veins are patent. Certainly the appearance of early skin changes at the ankle constitutes an adequate indication to urge the patient to have prophylactic surgery promptly The patient is warned preoperatively that other veins may dilate in the future that varicose veins require a reorientation of life activities in many instances, and that careful postoperative follow up measures are almost as important as is the surgery which usually cannot remove all varices let alone the predisposition to form varices

In making the upper (inguinal) incision,

it is important to avoid severing the numerous lymphatic channels (incise skin and then spread the fatty tissues), else a simple procedure may result in prolonged morbidity as the wound drains lymph for weeks and perhaps becomes infected It is of course far simpler to strip the lower portion of the long saphenous from below upward than from above downward to the ankle, since the former direction allows one to invert the smaller portion of the vein into the larger portion as the vein ascends It is important to identify preoperatively the sites of the more prominent collateral varices (with special note of those which are most offensive to the patient) and to mark these carefully, either with an indelible substance which will not be washed off as the leg is prepared for operation or, better still, with the scratch mark of a pin Otherwise, both the patient and the operator may be dismayed when prominent varices are present postoperatively Patients are advised to wear elastic stockings for weeks or months following the operation, certainly until ankle swelling or induration has subsided

In studying the causes of recurrences of varicose veins, Luke[109] concluded that most are due either to the fact that incompetent communicating veins were missed at the initial operation or to the subsequent opening of incompetent communicating veins between the saphenous systems and the deep venous circulation If not dealt with, these incompetent communicating veins may result in recanalization of the original veins, or they may produce varicosities in formerly small superficial collateral venous channels

Chronic varicose ulcer This condition will be further discussed under the heading of *stasis ulcer* of the lower extremity, since in many patients who do not have well defined varices it is impossible to determine the extent to which varicose veins contribute to the ulceration, as compared to deep venous disease In either case, the fundamental defect appears to be venous stasis, with or without abnormality in lymphatic drainage

THROMBOPHLEBITIS AND POSTPHLEBITIC SEQUELAE Thrombophlebitis may initially begin as "phlebothrombosis," since it is claimed that thrombosis in a vein almost invariably results in at least a degree of surrounding inflammation Yet, even so, the condition usually diagnosed as thrombophlebitis, with its inflammatory and adherent thrombus, is not accompanied by the same hazard of pulmonary embolism as is the condition that has come to be known as phlebothrombosis, with its bland and readily dislodged thrombus Hence, the distinctive terminology does serve a useful purpose, it seems to us Phlebothrombosis and pulmonary embolism are discussed elsewhere (p 499), and here only thrombophlebitis will be considered

Etiology of thrombophlebitis Thrombophlebitis may appear following direct injury to the vein, or as the migratory phlebitis of thromboangiitis obliterans, or under less readily explained circumstances Varicose veins are particularly susceptible to the etiologic agents, known and unknown, which may cause thrombophlebitis, but it is the thrombosis of the deep veins of the legs or pelvis which produce the most marked clinical changes These thromboses are particularly likely to occur following operation or childbirth, but they are also frequently observed when the patient has a "medical" disease, among the more notable ones being pancreatic disease and malignant tumors Yet, "spontaneous" thrombophlebitis is often encountered whose etiologic basis is not identified Thrombophlebitis may occur in patients with blood dyscrasias or with pelvic masses which press upon the iliac veins A suppurative condition adjacent to large veins, as occurs in postpartum sepsis, may also result in thrombophlebitis Even so, a great many cases of thrombophlebitis have little etiologic explanation, as noted above

Signs, symptoms, and diagnosis of thrombophlebitis In contradistinction to phlebothrombosis, in which the first manifestation may be a pulmonary embolus with the signs and symptoms thereof, thrombophlebitis usually is manifested primarily in the in-

volved extremities. There is usually swelling of the part, which can most readily be determined by measuring the extremity and comparing this value with that of the opposite member at the same level There is generally some pain, associated often with tenderness redness, increased local temperature, and fever As the more acute reaction subsides the redness or increased temperature of the extremity may be replaced by a chronic edematous swelling which actually renders the leg somewhat cooler than the normal one. Occlusion of the deep veins may be demonstrated by angiogram.

Actually, however the diagnosis of acute phlebitis or thrombophlebitis is usually not difficult, since definite and characteristic physical findings are typically present in the involved extremity

Management of acute thrombophlebitis The patient is kept at bed rest with the legs elevated, and elastic bandages are applied from the toes to the groin. Anticoagulants are frequently employed often beginning immediately with adequate doses of heparin and at the same time starting Dicumarol or a related compound. In general it will be necessary to give approximately 50 mg. of a *long acting (a slowly released)* heparin compound every 6 hours intramuscularly, controlled by the determination of the clotting time, the usual 3 tube method being clinically adequate. A clotting time of not less than 20 minutes and not greater than 1 hour constitutes satisfactory control Patients vary considerably in their response to heparin, and the clotting time in the individual subject will also vary according to the time of the last injection

Whereas the effect of heparin in lowering the rate of clotting begins in a few minutes, the effect of Dicumarol (which diminishes clotting by a specific toxic effect on the liver to reduce the production of prothrombin) is not achieved for from 2 to 3 days. Initially both heparin and Dicumarol are given, the rapid action of heparin produces the desired anticoagulant effect until the cheaper but more slowly acting Dicumarol can take effect. Heparin, which must be injected, is then discontinued One may give 300 mg. of Dicumarol or a related compound by mouth initially, 200 mg. the following day, 100 mg. the third day On the third day the prothrombin level is determined and thereafter the dosage (perhaps 50 to 100 mg. per day or every other day) is regulated by a determination of the prothrombin level at judiciously spaced intervals The prothrombin level should be kept below 50 per cent but above 20 per cent of normal It is important to realize that some patients may exhibit spontaneous hemorrhage such as hematuria, at a much higher prothrombin level than do others It is important to obtain a baseline prothrombin measurement before Dicumarol is begun.

The rationale for using anticoagulants is, first to diminish the extent of the thrombosis in the extremity and second to diminish the likelihood of pulmonary embolism There are those who feel that anticoagulants have significantly diminished fatalities from pulmonary emboli whether arising from "bland thrombosis" or from frank thrombophlebitis As stated elsewhere we treated a patient with chronic venous disease of the legs who began again to have pulmonary emboli each time anticoagulants were stopped. Yet, for one such patient, there are many others in whom the value of anticoagulant therapy is open to genuine question. Furthermore definite hazards attend the use of anticoagulants the chief one being of course the occurrence of spontaneous hemorrhage which may be difficult to control Heparin can be promptly neutralised by the injection of protamine, milligram for milligram. Also the newer forms of vitamin K_1, injected in massive doses have been shown significantly to diminish if not to abolish the affect of Dicumarol. Nevertheless, almost all clinics using anticoagulants freely have at times had difficulty with hemorrhage. This is not such a disadvantage as to render the use of these agents unwarranted but it is certainly a matter to be considered in patients where hemorrhage from

various organs might be unusually damaging

Antibiotics are used if the patient with thrombophlebitis manifests chills and fever

Active *surgical intervention* may be required if pulmonary emboli arise from an extremity which is obviously the site of venous disease The offending vein is ligated proximal to the thrombosis, if feasible Thrombophlebitis may involve the major pelvic veins, and upon occasion septic emboli may produce lung abscesses and septicemia Under these circumstances, in at least one case with which we were associated, ligation of the inferior vena cava abolished further emboli and the patient rapidly improved

THE POSTPHLEBITIC SYNDROME CHRONIC VENOUS INSUFFICIENCY Patients who recover from the acute episode of thrombophlebitis may gradually develop the condition that has come to be termed chronic venous insufficiency or the postphlebitic syndrome This consists of chronic pain and swelling of the extremity that is aggravated by the upright position, eventually cellulitis, an eczematoid reaction of the skin, and, finally, ulceration of the lower leg may appear The ulcer which develops from the chronic cellulitis of the lower leg has been termed a "stasis ulcer," and in a great many patients it is difficult to determine whether the ulceration has been due primarily to deep vein thrombosis, to varicose veins, or to a combination of both While either may result in a stasis ulcer, it is perhaps fair to say that the underlying pathologic feature of both consists of deranged venous dynamics in the lower extremity, perhaps associated with occlusion of the lymphatics by chronic cellulitis, as has been recently reemphasized by Moyer and Butcher[115]

To recapitulate, the postphlebitic syndrome may be manifested by stasis ulcer in the absence of readily demonstrable varicose veins Varicose veins may precipitate the development of a stasis ulcer in the absence of deep vein occlusion by thrombosis Both may be present and contribute to the development of the stasis ulcer F neither of these defects may be demons in many patients who have ulceration the ankle In fact, in perhaps a major "leg ulcer" patients who do not hav vious varices the etiology of the stasis is quite obscure

PRINCIPLES OF MANAGEMENT OF STAS CERS OF THE LOWER LEG *Prophylaxis an servative measures* So difficult is achieve truly satisfactory results once vere stasis ulcer has developed that highly desirable to avoid this complic For this reason, varicose veins shou treated before chronic recurrent cellul the inner aspect of the lower leg has allowed to progress to ulceration If u tion has occurred, then the treatment ulcer itself will be similar to that desc below for the postphlebitic ulcer

In the patient with acute deep thro phlebitis every effort is to be mac achieve the greatest possible recovery the initial attack While there are very nite limits to what may be accompli depending upon the circumstances of th dividual patient, it is advisable to trea initial attack of thrombophlebitis vigor by the use of bed rest, antibiotics, anti ulants, and elastic stockings or band Thereafter, until all swelling disappears patient should be urged to remain witl feet in an elevated position for at lea portion of the day to avoid serious swe from venous edema in the lower extrei Recurrent attacks of thrombophlebitis similarly managed with care, always w view to the much worse circumstances will exist if the condition progresses to tual ulceration, despite the impatienc the patient with the conservative meas He should be made to understand tha has a chronic disease which is not rea "curable" in the usual sense, and whicl quires new habits Even so, the cond usually does improve in time, and th the justification for cautious optimism encouragement of the patient to adoj hopeful attitude

Operative treatment of stasis ulcers The desirability of high saphenous ligation and stripping, plus ligation of the short saphenous vein for varicose ulcer, has been outlined However the ligation of the major veins for the treatment of the *postphlebitic ulcer*—as first advocated by Parona[170] in 1904, by Leriche[94] in 1923, and later re emphasized by Buxton and Coller[35] and by Linton and Hardy[106]—has not received the same general acceptance as has the ligation and stripping of the great saphenous vein for *varicose ulcer* The rationale for ligation of the superficial femoral vein for postphlebitic ulcer is that following thrombosis this vein recanalizes and thus, due to incompetent valves venous stasis occurs from back pressure, this back pressure being relieved by ligation of the vein Boyd and his associates[29] studied this procedure in 42 patients, 36 of them female and 6 male. The extremities were examined preoperatively with venous pressure recordings and phlebograms, and in some patients these studies were repeated following surgery In addition, careful evaluation of the arteries was made before operation The majority of the patients presented long-standing postphlebitic ulceration and were given a preoperative program of complete bed rest to reduce the leg edema as far as possible by elevation of the extremity The ulcer surface was treated by an occlusive dressing utilizing streptomycin, followed by frequent moist dressings after the gross infection had been controlled At operation either the popliteal or the superficial femoral vein was ligated, though in some the femoral vein itself was ligated at the same operation the ulcer was excised and the defect grafted Following operation the patients were restricted to bed until the grafted ulcers were finally healed and on leaving the hospital the extremity was supported with an elastic stocking or some similar support depending upon the degree of edema which followed mobilization. Since other criteria of improvement were somewhat intangible ulcer healing was selected as the most satisfactory clinical means of assessing the success or failure of any treatment. Maintenance of ulcer healing for 3 years, gross reduction in swelling, and a marked diminution in pain were classified as good results A deterioration was recorded if the original ulcer had broken down or enlarged or a further ulcer had appeared *de novo* Patients who had an increase in swelling or pain were also listed in the poor result groups. Of the 42 cases satisfactorily followed, 14 cases were classified as good and 8 of these had ulcers preoperatively Seven of these ulcers remained completely healed and the other ones had broken down to a minor extent after 2 years Boyd and his coworkers concluded that femoral ligations were the least unsatisfactory of the procedures, since 6 of 15 patients who had popliteal ligations exhibited great deterioration after the ligation In the 6 patients whose exercise venous pressure was reviewed both before and many months or years after popliteal vein interruption, a postoperative rise, indicating a less efficient venous clearance mechanism, was recorded in every case. It was found that, of 6 patients who had venous pressure recordings following exercise both before and following operation, in none was the postoperative pressure lower than the preoperative one and in some cases it was increased. Thus, it was concluded that ligation of the superficial femoral or popliteal vein resulted not in a decrease in the pressure in the veins of the foot or ankle but usually resulted in an increase in this pressure Accordingly, it was concluded that ligation of a major vein, and particularly the popliteal vein, hindered the venous return from the lower limb Improvement seen in their 14 patients who were classified as showing good results were thought to be more correctly attributed to the ligation of the incompetent superficial communicating veins skin grafting, excision of the ulcer, and supervision of the after care of those patients with particular emphasis upon re-education in view of their partial disability

These results have been cited in some detail because they coincide with the views of



Fig 177 Chronic stasis ulcer excised, with split thickness skin grafting Ulcers of the lower leg may be secondary to varicose veins or to deep vein phlebitis Yet, in a great many patients no varices or chronic deep phlebitis appears to exist, and the cause of the ulceration is obscure

the present writer In our experience with this procedure, which is admittedly small, ligation of the superficial femoral vein as a part of the treatment of postphlebitic ulcers has appeared to add little

Excision of stasis ulcer with skin grafting (*Fig 177*) If the objective is merely to provide covering of the ulcerated surface by epithelium, this can be achieved in many ulcers simply by placing the patient in bed with the legs elevated for a week or so Epithelium readily grows in from the sides, particularly after the infection has been diminished by local treatment with antibiotics and moist compresses, and an epithelial covering will be achieved Unfortunately, this epithelial covering overlies diseased tissues and promptly exhibits dissolution once the patient is on his feet again Therefore, the simple covering of an ulcer with a thin layer of epithelium, whether this is allowed to occur spontaneously with the patient at bed rest or whether a split thickness skin graft is applied to the ulcerated surface, will not rehabilitate patients with stasis ulcers There is an increasing awareness that the entire defective tissue must be excised, down to the fascia Moreover, excision of only the ulcer itself, without removing the diseased surrounding but still intact skin, will invite recurrence Moyer and Butcher[115] have advocated the injection of sky-blue dye (Wyeth) into the superficial or intradermal lymphatics to delineate the diseased from the normal skin The material spreads along the lymphatics when they are present and not occluded by chronic inflammation, but the dye does not enter and pass along the lymphatics of diseased skin Thus, if all tissue is excised back to the point at which normal flow of the dye occurs in the superficial skin lymphatics, then the chances of having the ulcer recur after deep and wide excision with ligation of communicating veins beneath are reported to be reduced

Following wide and deep excision of the ulcer and split-thickness skin grafting, the patient is kept in bed until the skin graft is well healed Then he is allowed up gradually, great care being taken to avoid the occurrence of small hemorrhages beneath the skin graft When the patient can be up and about with the skin graft remaining in an apparently healthy condition, he is allowed increasing amounts of exercise with the concurrent use of an elastic stocking up to the knee Here too, educational measures are important, and the patient must avoid undue swelling of this lower extremity, assuming the supine posture at all possible times during the first few months postoperatively A general rearrangement of his way of life thereafter may be required However, so disabling is the chronic ulcer that all these measures are well worthwhile

MISCELLANEOUS OTHER MANIFESTATIONS OF THROMBOTIC DISEASE OF VEINS Venous thrombosis may occur wherever veins are found, and several rather striking clinical conditions may result Again, venous thrombosis may be due to venous stasis, local venous injury, increased blood coagulability, infection, or invasion by tumors, it may occur following the use of diuretics, in blood dyscrasias such as polycythemia vera, and in the presence of certain tumors such as carcinoma of the pancreas

Occlusion of the inferior vena cava may be caused by simple thrombosis, thrombophlebitis, neoplasm, aneurysm, or ascites Most commonly the obstruction results from an ascending thrombus in one or both iliac

veins which we observed in at least three debilitated patients in one year There is swelling of both legs and the lower trunk, associated with marked distention of collateral venous channels such as the inferior epigastric veins which communicate with the superficial abdominal veins, including the internal mammary veins. Actual occlusion of both renal veins at the vena cava is not always incompatible with life, though reduced urine flow is associated with albuminuria and hematuria. In inferior vena caval obstruction the venous pressure in the legs is elevated, but that in the arms is normal Accordingly, the presence of prominent veins on the abdominal wall adjacent to the umbilicus does not necessarily mean that the patient has portal hypertension due to cirrhosis, they may also reflect obstruction of the inferior vena cava Upon occasion prominent abdominal veins may merely reflect the fact that the individual has lost much weight and supporting subcutaneous tissue particularly fat, which has allowed the veins to become more prominent. The ligated vena cava may recanalize [112]

When blood flows in a retrograde fashion through veins and causes their diameter to increase, the valves of these veins often become incompetent, if for no other reason than that the valves are no longer of such size as will completely occlude the lumen of the distended vessels.

Superior vena caval obstruction produces a striking clinical picture known as the superior vena caval syndrome. The resulting venous engorgement of the upper portions of the body drained by the superior vena cava results in cyanosis and edema of the face, neck arms and upper thorax. The eyes may become bloodshot and on leaning forward or other exertion headache dizziness and even fainting may occur Large distention of the veins of the upper portions of the body is apparent with a marked increase in venous pressure

The causes of superior vena caval "obstruction" are varied and among those that we have encountered were nonspecific mediastinal inflammation, tuberculous lymph nodes sarcoidosis, lymphoma such as that of Hodgkin's disease, extension of pulmonary carcinoma, metastatic disease from other tumors aneurysm, mediastinal goiter, constrictive pericarditis, and massive left pyothorax with a shift of the mediastinum to the right (Fig 208) In one patient the condition appeared shortly after he had lifted one end of an automobile on a bet, presumably the great exertion resulted in a type of "effort thrombosis" to be described below

The diagnosis of superior vena caval obstruction is usually easy, due to the distribution of the venous distention. However, angiography will demonstrate delayed emptying of the veins of the injected arm, extensive collateral drainage will be seen and not infrequently the site of obstruction will be visualized.

The treatment and prognosis of obstruction of the superior vena cava depends upon the etiology For example, although neoplastic compression may be relieved by radiation the patient will not often be cured Where the condition is due to a chronic nonspecific inflammatory process with associated fibrosis neither x ray nor direct surgical attack is particularly successful The surgeon might think preoperatively that he will be able readily to remove the tissue which is compressing the vena cava, but at operation he finds it difficult to identify this vessel amid a dense inflammatory mass and he finds it even more difficult satisfactorily to remove all obstructing tissue from around it. The obstruction is usually not localized to one small segment, and resection with homografting is not often successful initially or for long.

There are now numerous reports in the literature of the use of vessel grafts more recently arterial grafts for bypassing the obstruction of the superior vena cava. This has allowed satisfactory decompression in some instances but again successful results are usually short lived because of the nature of the underlying disease process

"Effort" thrombosis of the axillary vein is a particularly interesting condition which occasionally is seen following some unusual or violent physical effort, "as following spanking of a child" Surprisingly, pulmonary embolism has occurred only with the greatest rarity following thrombosis of the axillary vein The physical findings include an increase in the circumference and cyanosis of the involved arm The superficial veins are distended, and the tender and firm axillary vein is palpable in the axilla

No particular therapy other than general supportive measures is required The thrombosis does not tend to propagate, and the symptoms usually subside within a few days or weeks

Acute massive venous occlusion in the lower extremity has been reported under the appellation of "phlegmasia cerulea dolens" This condition has been recognized for a great many years and, according to Osius,[110] it was first described by Fabricius Hildanus in 1593, when he reported and described such an entity, even to the details of gangrene Many causes have been described, the most common being surgical and obstetrical procedures, infection, malignancy, and traumatic accidents It may be difficult to distinguish venous occlusion from arterial occlusion in some patients, for arterial occlusion can be associated with significant swelling of the extremity [19]

The *pathologic physiology* of acute massive venous occlusion appears to consist of virtually complete obstruction of the venous outflow of the involved leg This results in a diminution of arterial inflow, in addition to the fact that arterial vasospasm may be intense

The diagnosis is suggested by the rapidity with which the thrombosis occurs and by the obvious thrombosis of the larger vessels of the leg

The *treatment* of the condition consists of paravertebral blocks or continuous caudal anesthesia to diminish arterial spasm and thus enhance blood supply to the leg, combined with elevation and wrapping of the extremity and the use of anticoagulant therapy Venous thrombectomy was utilized by Osius, and he considered it to be helpful

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Chapter 16

The Lungs

All systems of the body comprise a single functional unit, but certain units are functionally more intimately related than are others The heart and the lungs constitute an exceedingly well synchronized complex, the activity of one closely influencing that of the other It is therefore not surprising that one frequently hears the combined term "cardiopulmonary function," instead of "heart function and lung function " Nevertheless, if it is constantly borne in mind that the two activities are interdependent, then it is perhaps permissible to discuss lung physiology separately for the sake of clarity

The normal and pathologic physiology of the lungs will be discussed under the following headings

- A The physiology of respiration
  - 1 Control of pulmonary ventilation
    - a Nervous control
    - b Chemical control
  - 2 Mechanics of pulmonary ventilation
    - a Muscles of respiration
    - b Intrapleural pressures
    - c Cough mechanism
    - d Hiccups
    - e Methods of artificial respiration
  - 3 Functional anatomy of the lungs
    - a The pulmonary segments
    - b Blood supply to the lungs
  - 4 Lung volumes and capacities
  - 5 Lung function tests
- B The pathophysiology of certain representative thoracic conditions
  - 1 Respiratory dysfunction due to excision of pulmonary tissue
  - 2 Indications and value of pulmonary decortication
  - 3 Abnormalities of the pulmonary circulation further comment
  - 4 Acute and chronic pulmonary emphysema
  - 5 Intrathoracic tumors
  - 6 Lung cysts
  - 7 Chronic pulmonary infection bronchiectasis, lung abscess, and tuberculosis
  - 8 Thoracic trauma
  - 9 Severe hemoptysis causes and management

The Physiology of Respiration

Control of Pulmonary Ventilation

NERVOUS CONTROL The nervous control of respiration is influenced by many factors, and numerous of these are still obscure The primary respiratory center that is concerned with automatic rhythmic respiration is situated in the pons and the upper medulla However, the localization of the respiratory center is not complete, for a large number of neurons in this general region appear to be integrated in the function of respiration There is evidence that on either side of the medulla there is a group of neurons which may influence respiration on the opposite side, and there is also evidence to suggest that the respiratory center may contain both an *inspiratory center* and an *expiratory center* Normally, regular and rhythmic respiration would seem to be produced by a rhythmic stimulation of the inspiratory cen-

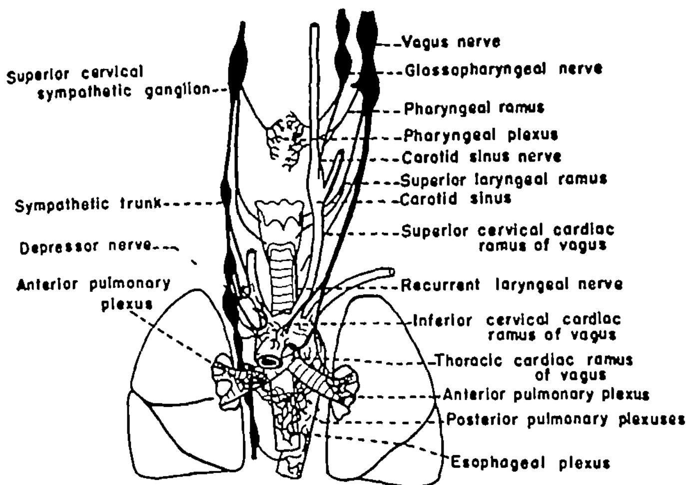


Fig 178 Vagus (*right*) and sympathetic (*left*) nerves of the respiratory tract. The precise rôle of the autonomic nervous system in respiration has never been clearly defined Thus, pulmonary denervation for such diseases as emphysema and bronchial asthma must be viewed with reserve (From KUNTZ, A. *Visceral Innervation and Its Relation to Personality* Springfield Ill., Charles C Thomas, 1951)

ter, expiration then occurring as a passive movement. Yet, it is of course apparent clinically that expiration can be a conscious and a forced effort—as in asthma, emphysema or severe exercise. Furthermore, there may be cross connections between the inspiratory and the expiratory centers, since the stimulation of one can produce inhibition of the other The inspiratory center apparently lies in close contact with the central origin of the vagus nerves and certain of these relationships are shown in Figure 178

The question of whether or not there is spontaneous activity of the respiratory center has been a subject of much debate. There are those who feel that the respiratory center does not have spontaneous or automatic activity and they feel that the reflexes arising peripherally which constantly act upon the center are responsible for the apparently rhythmic activity Recent evidence obtained by Howard and Webb[11] in our laboratory favors this view These workers divided all but one afferent nerve from the lungs, and respiration continued However, when this last afferent nerve was sectioned, the dog abruptly ceased to breathe and died if not mechanically ventilated. These studies would appear to provide recent evidence that even if the respiratory center should have some degree of spontaneous rhythmic activity, it is not enough in dogs to maintain life.

The *respiratory center* is acted upon by, and in turn influences, various and sundry reflexes particularly those involving the circulation. In addition respiration is quite sensitive to psychic impulses, and this provides the stimulus for certain "hyperventilation" syndromes of emotional origin.

There is a subsidiary "respiratory center" which includes the reflex arc of the motor cells of the anterior horn of the spinal cord The anterior horn cells coordinate principally the action of the respiratory muscles, they do not coordinate respiration as a whole

Some of the central or higher center responses which may influence respiration are as follows (1) laughing and crying, (2) sneezing due to irritation of the nasal mucous membrane, conducted by the sensory fibers of the Vth cranial nerve, (3) a related sneezing reflex known as the nasociliary reflex, which is activated when one enters bright sunlight, the sensation of nasal irritation being produced, (4) startling sounds or the viewing of upsetting scenes, and (5) even sudden unpleasant thoughts Nevertheless, under ordinary circumstances these factors assume a relatively minor rôle in the regulation of respiration The most important factors are *reflexes* from the lungs and the carotid and aortic "sinuses," and *chemical* changes in the blood which involve pH and CO_2 tension (see below)

Pulmonary vagal reflexes The *vagus nerves* (Fig 178) have a rich plexus in the lungs The end organs are stretch receptors, and are stimulated particularly during inspiration As inspiration begins, the number of impulses going to the respiratory center is markedly increased The increasingly rapid bombardment of the inspiratory center in the medulla by these impulses set off by stretching of the lungs finally inhibits inspiration Expiration, usually passive, then occurs due to the elastic tissue of the lungs However, in certain diseases, notably bronchial asthma and chronic pulmonary emphysema, expiration becomes an active effort even at rest Hering and Breuer described these pulmonary vagal reflexes in 1868

Other reflexes which influence respiratory efforts aortic and carotid sinuses and bodies Other reflexes which may affect respiration, particularly under abnormal conditions, are those which arise from the aortic arch and from the carotid sinuses situated at the bifurcation of the carotid arteries In 1927 Heymans and Heymans[10] reported that respiratory reflexes could be elicited from the aortic arch (Fig 179) Thereafter it was found that stimulation of structures in the region of the carotid bifurcation also could influence respiration It was subsequently shown that both the carotid bifurcation and the aortic arch contain two types of receptors, the *pressoreceptors* which respond to mechanical stimulation and the *chemoreceptors* which respond to chemical stimulation A rise in arterial blood pressure stimulates the pressoreceptors and tends to diminish respiration In contrast, stimulation of the carotid and aortic bodies, which contain small glandlike structures that are stimulated by oxygen lack, tends to increase respiration Again, except under abnormal conditions these pressoreceptors and chemoreceptors have comparatively little to do with respiration The pressoreceptors almost never have a significant part in normal respiration, but the chemoreceptors (which are stimulated by anoxemia but little influenced by carbon dioxide tension) exert a protective effect of considerable importance in patients whose respiratory center has become insensitive to changes in carbon dioxide tension and hydrogen ion concentration When the arterial oxygen tension has fallen to approximately 70 mm Hg in man (normal level, 95), impulses arise from the aortic and carotid bodies which stimulate the respiratory center to increase inspiration

CHEMICAL CONTROL The chemical control of pulmonary ventilation was reviewed by Winterstein[23, 24] Whereas the chemoreceptors are particularly sensitive to anoxemia but only slightly sensitive to carbon dioxide tension, the respiratory center is markedly sensitive to changes in carbon dioxide tension and hydrogen ion concentration but relatively insensitive to changes in arterial oxygen saturation

The rôle of carbon dioxide Respiration must prevent anoxia and must assist in the

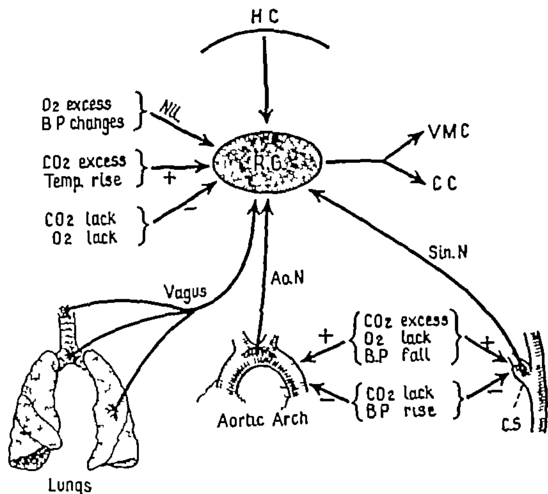


Fig 179 Regulation of respiration. R.C = Respiratory center H.C = Higher centers C C = Cardiac center V.M.C. = Vasomotor center CS = Carotid sinus region (including carotid body) Sin.N = Sinus nerve Ao.N = Aortic nerve (aortic arch includes the aortic body) + = Stimulates breathing − = Depresses breathing The bronchioles are well supplied with smooth muscle but the musculature of the pulmonary arterioles is in doubt. It is possible that alterations in pulmonary resistance are effected more by changes in bronchiolar tone and diameter than by changes in vascular tone (From WRIGHT S *Applied Physiology* Ed. 9 London, Oxford University Press 1956)

maintenance of the normal blood pH The chemical control of respiration is dependent largely upon the effect of carbon dioxide upon the respiratory center Anoxia, on the other hand, has a depressant effect upon the respiratory center though anoxemia may stimulate the respiratory center reflexly through its effect upon the aortic and carotid bodies Whereas the respiratory center may have as noted previously, a degree of inherent rhythmicity it is extremely sensitive to changes in blood carbon dioxide tension. Very slight increases in the concentration of carbon dioxide result in an increased respiratory volume exchange and decreased concentrations of carbon dioxide result in a diminished respiratory volume exchange. When the respiratory center is depressed by anesthesia or anoxia and cannot respond adequately to an increasing carbon dioxide tension a very dangerous state of acidosis and anoxemia may result. Serious respiratory acidosis may also occur in emphysema.

CO_2 tension versus blood pH as a respiratory stimulus Much debate and experimentation has centered around the effort to determine whether the respiratory center is sensitive to the molecule of carbon dioxide *per se* or whether it is primarily sensitive to changes in hydrogen ion concentration and thus sensitive to carbon dioxide in that it has an acidifying effect. It is not necessary to present here the various types of data adduced to support the different views,

but there does appear to be evidence which would indicate that both the hydrogen ion concentration and the molecular configuration of carbon dioxide exert an effect upon the respiratory center Carbon dioxide may act also by stimulating the chemoreceptors in the aortic and carotid bodies When the hydrogen ion concentration of the arterial blood reaching the respiratory center is lowered (pH increased), the respiratory retention of carbonic acid assists in restoring the blood pH to normal (7 4) The opposite process obtains in acidosis This extremely important aspect of respiratory function—the elimination or retention of carbon dioxide, as required, in states of acid-base imbalance—was previously discussed in some detail (p 40)

Mechanics of Pulmonary Ventilation

It has been seen that the primary *afferent impulses* in respiration course through the vagus nerves, though some sensory fibers do course through the phrenic nerves (reflected in pain referred to the shoulder in diaphragmatic irritation) The *motor impulses* for respiration travel from the respiratory center to the anterior horn cells of the spinal cord which, through reflex associations, coordinate the muscles of respiration

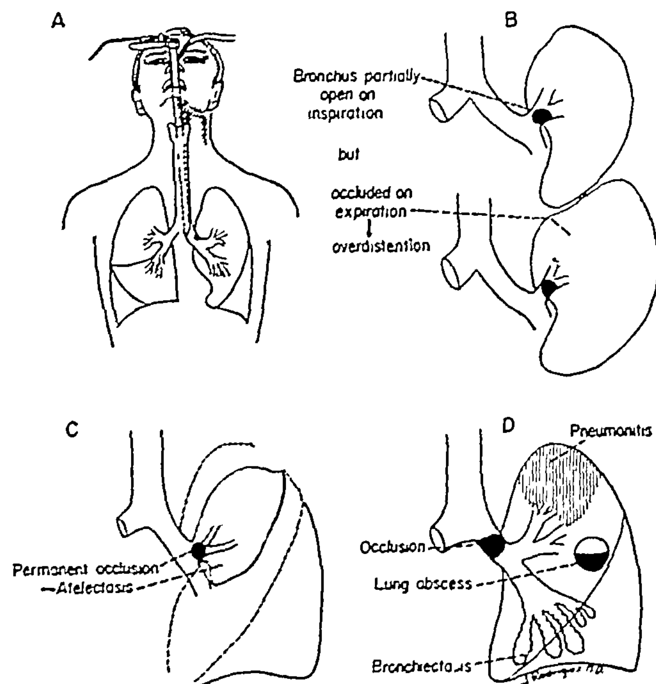


Fig 180 Lobar emphysema, atelectasis, and pulmonary suppuration are sequential developments in the course of progressive bronchial occlusion by tumor or foreign body

MUSCLES OF RESPIRATION The chief muscles of respiration are the diaphragm and the external intercostal muscles which, when stimulated by means of the phrenic and intercostal nerves, enlarge the chest both from above downward and in the transverse and anteroposterior dimensions This enlargement of the space within the thoracic cage results in a tendency for the thoracic wall and diaphragm to move away from the lung However, this increases the negative intrapleural pressure and causes the lung to follow the contours of the expanding thorax, and air is drawn into the lungs through the trachea Actually, the intrapleural space is normally but a potential space between the visceral and parietal pleurae, containing only a slight amount of lubricating fluid It was noted above that the recoil of the lung, which causes expiration, is due largely to the elasticity of this organ, upon which capacity is based the measurement of "lung compliance"

That bronchi as well as alveoli enlarge on inspiration can be readily observed at bronchoscopy during inspiration the caliber of the bronchi increases and during expiration the caliber of the bronchi decreases (Figs 180*B* and 199) The internal intercostal muscles may actively assist expiration

Exercise and increased respiratory requirements action of accessory muscles When more than the normal quiet respiration is needed, certain accessory muscles of respiration are brought into action During inspiration these include the serratus magnus, scaleni, trapezius, rhomboids, and alae nasi, in active expiration, the internal intercostals are assisted by muscles of the abdominal wall, which force the diaphragm upward

Pulmonary ventilation can be sustained by either the external intercostal muscles or the diaphragm, but the loss of both, through

paralyzing disease or excessively high spinal anesthesia, results in a situation in which ventilation must be carried on artificially

Although the diaphragm is the chief muscle of respiration and normally is responsible for a substantial portion of the respiratory volume, this muscle may be more or less fixed in one position in some individuals and then ventilation is achieved largely through the action of the external intercostal muscles. The previously mentioned accessory muscles of respiration may also be called into play

INTRAPLEURAL PRESSURES. In the physics of pulmonary ventilation, the intrapleural pressure is of the utmost importance. As has been emphasized, the intrapleural "space" is usually only a potential space, but under pathologic conditions it may become filled with pus, effusion, blood or air

The normal intrapleural pressure is slightly below atmospheric pressure, that is, there is a partial vacuum in the intrapleural space (from −9 to −12 cm. *of water* during inspiration and from −3 to −6 cm during expiration) The presence of this negative pressure maintains the lungs in their expanded state, during both inspiration and expiration. Were it not for this negative pressure or suction effect the constant pull of the elastic fibers of the lungs would collapse the lung (atelectasis) For, even in expiration the lung is by no means collapsed since a complete collapse of the lung reduces the lung size to only a fraction of the size it assumes in normal expiration (Fig 181)

The fluctuations in intrapleural pressure during the ventilatory cycle may be readily observed by introducing into the pleural space a needle connected to a water manometer, the variations in pressure are obvious The same fluctuations are seen in the underwater drainage tube inserted following a thoracotomy (Fig. 182) if the tube is not occluded the column of water in the tube may be seen to rise during inspiration and to fall during expiration.

Pathologic variations in the intrapleural pressure are discussed in some detail later on, including those in pneumothorax pyopneumothorax (Fig. 183), atelectasis and the pressure relationships which follow the removal of a lung

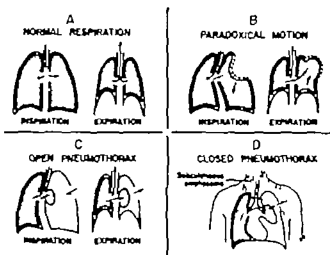


Fig 181 Paradoxical motion (*B*) not only interferes with the lung on the injured side but it also prevents effective expansion of the opposite lung. Furthermore "used" air tends to pass back and forth from one lung to the other and asphyxiation can occur The effects of open pneumothorax are similar to those of paradoxical motion, and venous return to the right heart may be diminished in both Closed "tension" pneumothorax can produce atelectasis of one lung and can seriously impair function of the other (see also Fig 182)

COUGH MECHANISM. While ciliary action of the bronchial epithelial cells will rid the normal individual of some amount of mucus or foreign material which the bronchi might contain this is entirely inadequate when a life-threatening amount of secretion or other material is present (Fig 184) Both reflex and voluntary coughing are most *important* in clearing the tracheobronchial tree of potentially occluding materials and thus avoiding *pneumonitis*, atelectasis bronchiectasis, or lung abscess *In the comatose* patient the cough reflex may not be sufficiently active *to open the* air passages and tracheobronchial *suction is f*requently mandatory It is also required in the noncomatose individual who because of discomfort or other *reasons* will not cough sufficiently to clear the smaller bronchi and prevent atelectasis and pneumonitis Actually, a chief *value of catheter* suction in most patients is that it stimulates the afferent vagal fibers

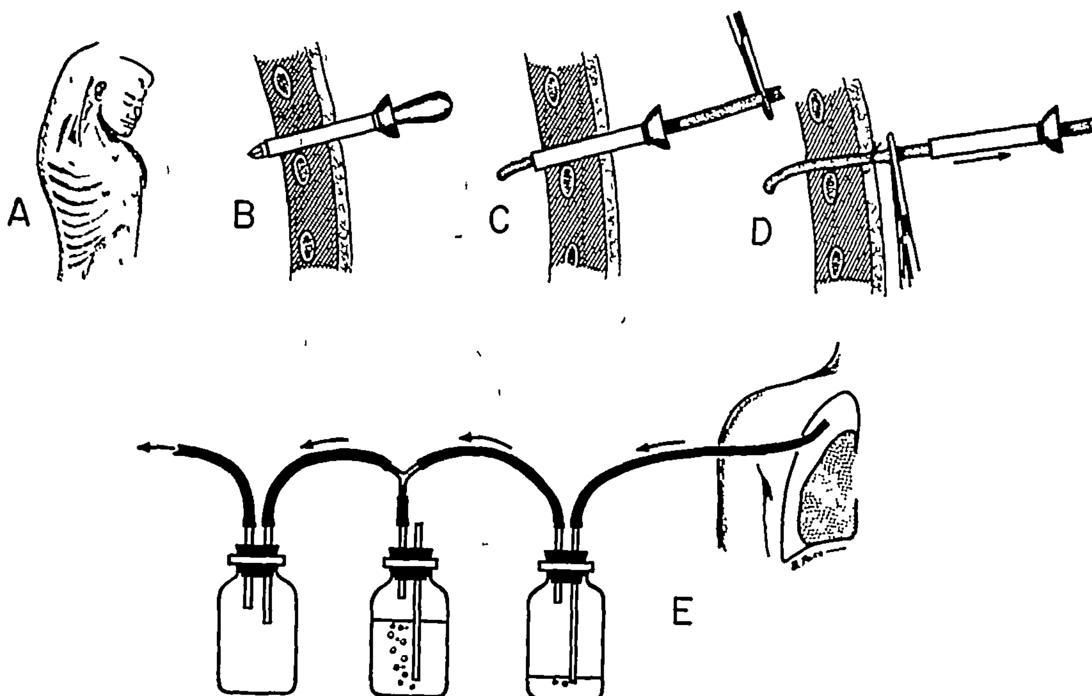


Fig 182 Management of tension pneumothorax In an emergency it is advisable to aspirate the hemithorax with a large needle to improve respiration Formal closed drainage can be instituted later



Fig 183 Massive left pyopneumothorax This patient had edema of the lower half of his body and the left upper half—but not the right upper half (see Fig 208) Following thoracentesis the edema promptly subsided

and produces involuntary coughing, which clears the smaller bronchi that one cannot expect to reach with either the catheter or the bronchoscope Moreover, after one session of suctioning, the patient usually coughs to avoid a second one

The act of coughing is initiated by a sharp inspiratory effort, followed by abrupt closure of the glottis and a forceful expiration which rapidly increases the intrapleural pressure, followed by sudden opening of the glottis so that the offending material is propelled upward toward the mouth When one is "coughing out" a patient, it is essential to insist that the patient actually close the glottis and thus generate an effective expulsive force In other words, merely to breathe deeply is not to cough

To appreciate the value of effective coughing, one needs but to auscult the poorly ventilated patient's chest and note the scattered râles and faint breath sounds in the dependent portions of the lungs Following this, the individual is asked to cough several times If one then listens again, he will usually hear fewer râles and much improved breath sounds, reflecting ventilation of previously atelectatic portions of the lung

Another factor in the pathogenesis of postoperative atelectasis is the diminished respiratory excursion caused by incisional pain Still another factor is the excessive use of opiates, these drugs reduce the sensitivity of the bronchial mucosa and may thus abolish the cough reflex Moreover, opiates also have an almost specific depressant effect upon the respiratory center This may re-

sult in an additional reduction in ventilation Thus, the accumulation of secretions because of an obtunded cough reflex, plus an inadequate ventilatory effort due to respiratory center depression, may produce serious anoxia and may even cause death in elderly subjects. If one doubts this effect, he can convince himself by determining arterial O_2 and CO_2 values in preoperative patients who have received perhaps 15 mg of morphine sulfate as preoperative medication, a not unusual dose in many parts of the United States The arterial oxygen saturation will often be depressed.

HICCUPS (HICCOUGHS, SINGULTUS) Hiccups are reflex spasmodic contractions of the diaphragm and often are due to gastric retention. They may be observed following thoracic and abdominal operations, in the presence of subdiaphragmatic inflammatory processes in states of acid base imbalance, with brain lesions, or with no demonstrable pathology When diaphragmatic irritation is the cause of the hiccups, the afferent impulses may be transmitted through the phrenic nerve or through other afferent nerves such as the vagus or sympathetics The motor limb of the reflex arc is supplied by the phrenic nerve

Despite the large number of remedies which have been suggested for the relief of hiccups this complication can present one of the most challenging problems in all of therapeusis. Some bouts of hiccups will respond to the usual measures such as the inhalation of carbon dioxide (paper bag rebreathing or CO_2 from a cylinder), or the spraying of the posterior pharynx with ethyl chloride or of course gastric decompression. There are other intractable cases of hiccups, however which may persist for days weeks or even months Formerly it was often necessary to inject or to crush the phrenic nerve on the side affected after identifying the involved hemidiaphragm at fluoroscopy Fortunately *chlorpromazine* has proved gratifyingly effective in controlling hiccups

METHODS OF ARTIFICIAL RESPIRATION While there is always available somewhere in most hospitals an anesthesia machine or pulmotor of some type for inflation of the lungs, such instruments are often not at hand and some immediate maneuver must be employed to maintain life These measures consist of mouth to mouth breathing and of the different technics of manual artificial respiration

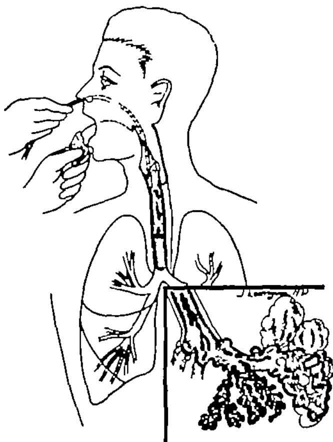
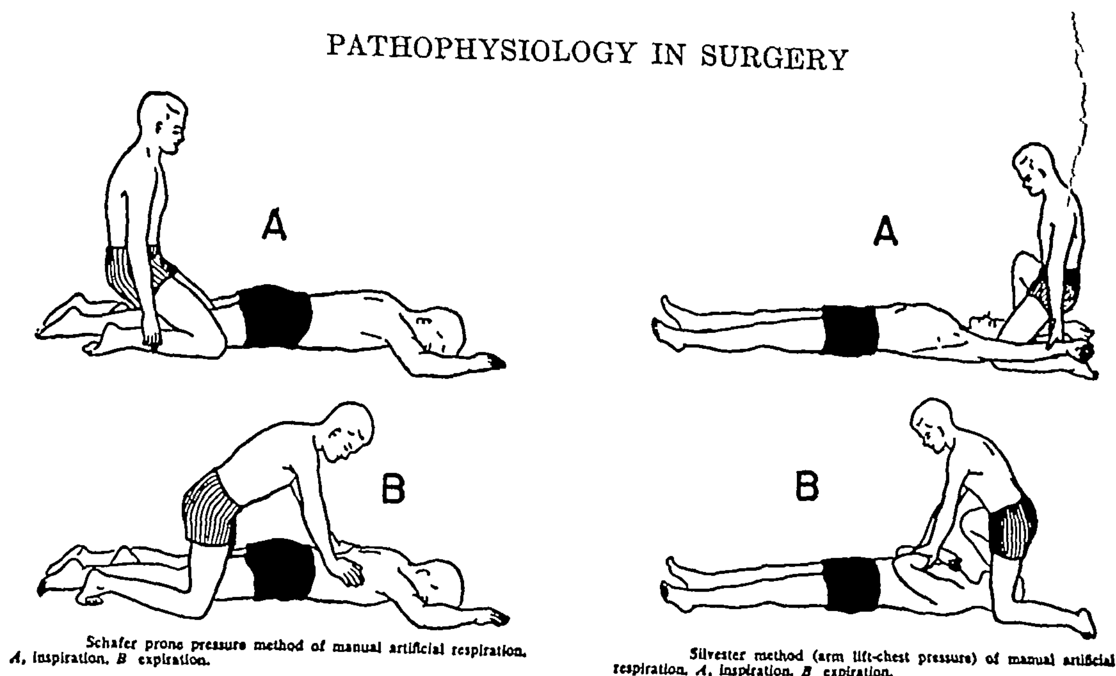


Fig 184 The patient should inhale as the catheter is advanced through the glottis In addition to the tracheal secretions aspirated with the catheter further material is cleared from the smaller bronchi by the highly important coughing that catheter suction stimulates.

Several studies in recent years have thrown considerable doubt upon the well known and widely used Schafer prone method, though unquestionably this method has resulted in the saving of many lives in the past. After a critical survey of manual artificial respiration procedures Gordon and his associates* came to the conclusion that one of the push pull methods (Fig. 185) was preferable in most instances. The conclusion was based upon studies in curarized



Schafer prone pressure method of manual artificial respiration. *A*, inspiration. *B* expiration.

Silvester method (arm lift-chest pressure) of manual artificial respiration. *A*, inspiration. *B* expiration.

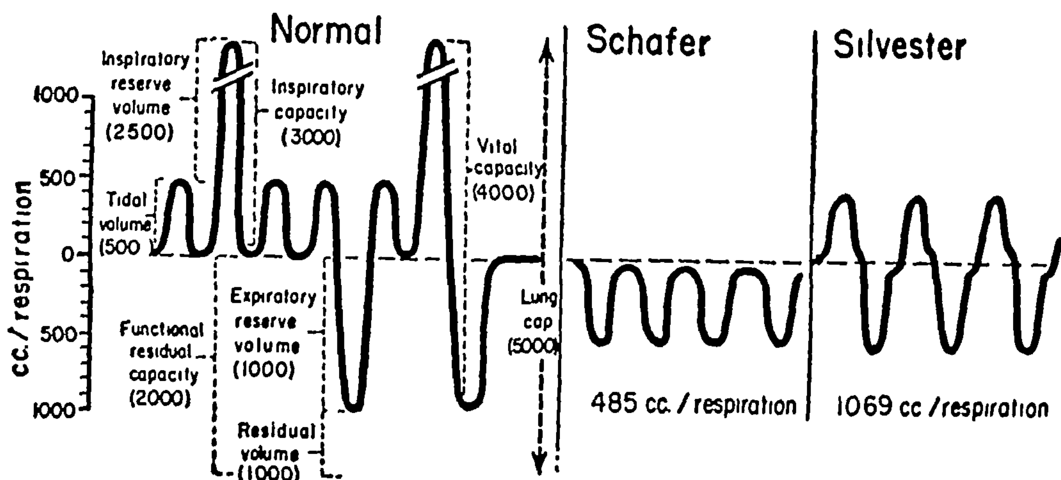


Fig 186 The Silvester method afforded a volume of 1069 cc per "respiration" as compared with 485 cc per respiration for the Schafer method (see text) (From GORDON, A S, SADOVE, M S, RAYMON, F, AND IVY, A C Critical survey of manual artificial respiration J A M A, **147** 1444, 1951)

normal subjects and upon warm corpses, in which the volume of air moved per minute by the different types of artificial respiration was measured These values are also shown in Fig 186 The Schafer method resulted in an exchange of only 485 cc of air per cycle, while the Silvester and the various lift-pressure methods resulted in the movement of approximately 1000 cc of air per cycle The conclusion of Gordon and his associates was that as soon as is compatible with the instructional requirements involved, the Schafer prone pressure method of manual artificial respiration should be replaced by one of the more efficient push-pull methods

Functional Anatomy of the Lungs

PULMONARY SEGMENTS (FIGS 186 AND 187) Pulmonary surgery has moved through a succession of stages, each succeeding stage being made possible by further advances in our knowledge of the underlying anatomy, physiology, and pathology of pulmonary conditions It was not until late in the 1930's that the method of massive tourniquet ligation of the pulmonary hilum was gradually abandoned in favor of the individual identification and ligation of specific structures in anatomic dissection It was not long thereafter that the resection of pulmonary lobes was performed with precision and with good results Next came the work of Churchill

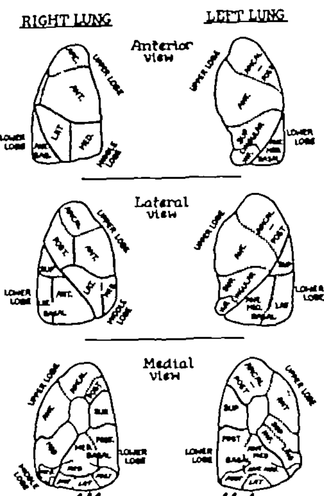


Fig 188 The pulmonary segments. (From JOHNSON J AND KIRBY C K *Surgery of the Chest* Chicago, Year Book Publishers, Inc., 1952)

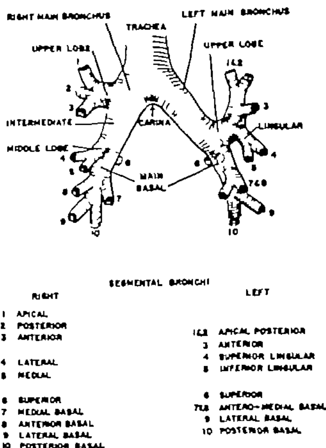


Fig 187 The pulmonary segmental bronchi (From JOHNSON J., AND KIRBY C K. *Surgery of the Chest* Chicago, Year Book Publishers, Inc 1952)

and others which gave impetus to the realization that the pulmonary segments were separate anatomic units (Fig. 188) and that they could be individually excised at operation. This also was an important advance, for certain diseases, notably pulmonary tuberculosis and lung abscess, tend to have a segmental distribution.

Each segment has its own bronchus artery and venous drainage, and with appropriate preoperative roentgenograms the disease can often be localized in a specific segment. Therefore the modern surgeon must have an intimate knowledge of the hilar structures of each individual segment, with the possible exception of the basal segments of each lower lobe. The segmental terminology proposed by Jackson and Huber[12] has been widely accepted in the need for a uniform nomenclature. The right lung has 10 segments and the left lung has 8 segments, the reason being that the apical and posterior segments of the left upper lobe arise from a common bronchus Nevertheless, the apical and the posterior segments of the left upper lobe can still be isolated and resected separately Two of the left basal segments are often fused, accounting for only 8 segments in this lung. The individual basal segments are usually not resected separately, though this can be done when it is necessary to preserve all possible pulmonary tissue The greater the experience of the operator with segmental resections the more accurately will he be able to excise the desired tissue without injuring adjacent segments.

On bronchoscopic examination it is possible under the most favorable conditions to visualize all or most of the segmental orifices on both sides It may thus be observed whether or not mucus, pus, or blood



Fig 188 The pulmonary segments are anatomically distinct elements of pulmonary tissue *Above* Note the deep fissure and sharp demarcation of the superior segment of the right lower lobe (held with lung clamp) *Below* The hemostats hold an entire diseased pulmonary segment that has been carefully excised Pulmonary function is not significantly reduced by the precise removal of such diseased tissue

is emerging from any given segmental orifice. A familiarity with the location of the segmental bronchi, as seen through the bronchoscope, is of material assistance in the interpretation of bronchograms and in the identification of the various segments at thoracotomy

BLOOD SUPPLY TO THE LUNGS The pulmonary artery to a lung can be divided without resulting in necrosis of pulmonary tissue. This is because a main nutrient supply of the bronchi and the parenchyma comes from the bronchial arteries, which carry systemic or arterial blood In contrast, one cannot divide the pulmonary vein to a portion of the lung without running considerable risk of atelectasis and gangrene. This is due to the fact that, in contrast to the bronchial arteries, the bronchial veins are usually rudimentary structures, and as a rule they are not able to transport the blood away from the lung in the presence of ligated pulmonary veins. Nevertheless, it has been shown that considerable hypertrophy of the bronchial veins may occur under certain pathologic conditions (*e g*, in some instances of pulmonary hypertension), and may be responsible for the transport of a considerable volume of blood from the lung in question. In the course of pulmonary resection it is advisable to ligate the artery first, since this will diminish the blood trapped in the portion of the lung to be excised.

Lung Volumes and Capacities

To establish uniformity of nomenclature in respect to the names applied to the various lung volumes a group of American respiratory physiologists agreed in 1950 to use the following terms and definitions [17]

A. Volumes There are four primary volumes which do not overlap (Fig. 189)

1 Tidal volume or the depth of breathing is the volume of gas inspired or expired during each respiratory cycle (usually about 500–600 cc)

2. Inspiratory reserve volume (formerly complemental or complementary air minus tidal volume) is the maximal amount of gas that can be inspired from the end-inspiratory position.

3 Expiratory reserve volume (formerly reserve or supplemental air) is the maximal volume of gas that can be expired from the end-expiratory level

4. Residual volume (formerly residual capacity or residual air) is the volume of gas remaining in the lungs at the end of a maximal expiration.

B Capacities. There are four capacities, each of which includes two or more of the primary volumes (Fig. 189)

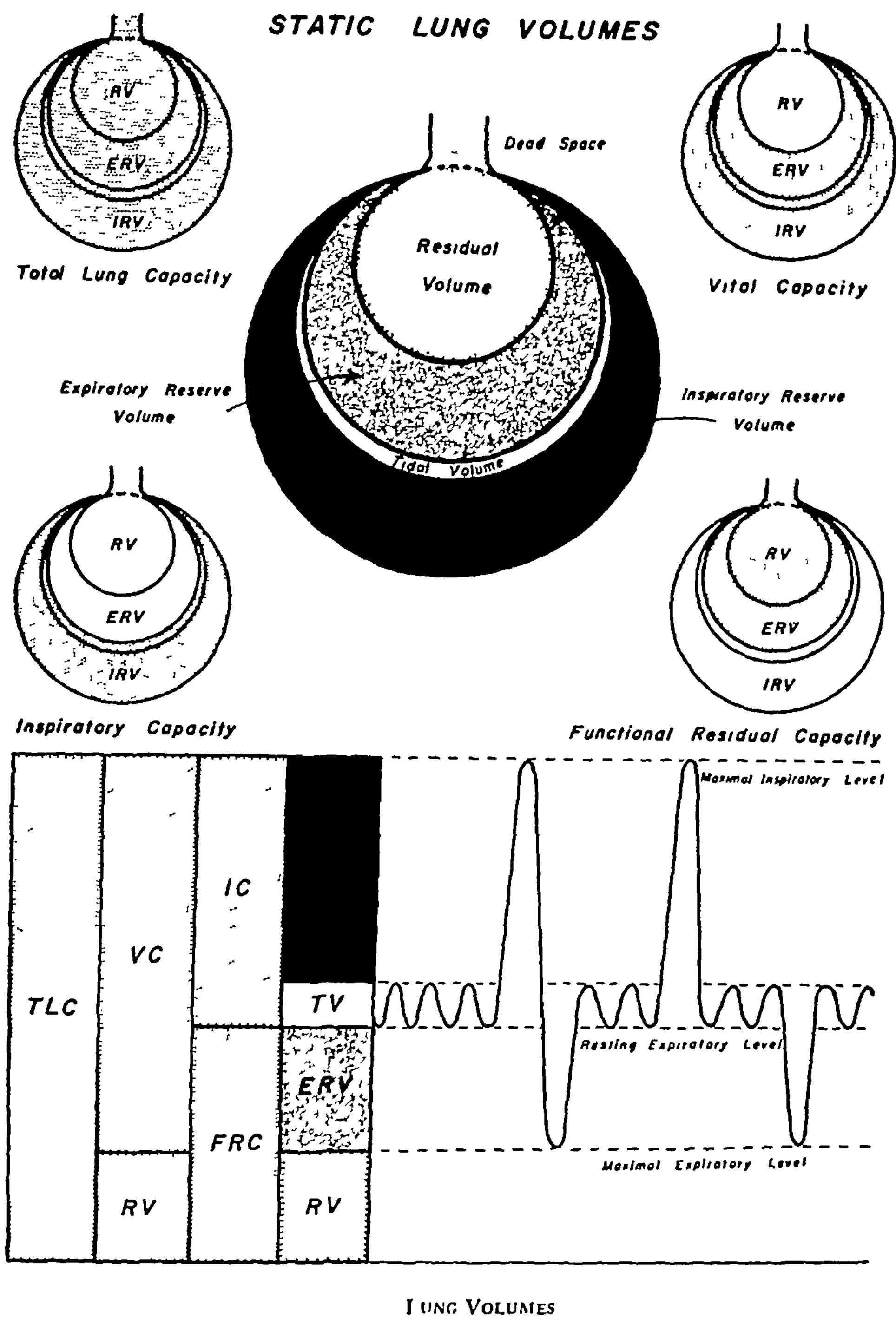
1 Total lung capacity (formerly total lung volume) is the amount of gas contained in the lung at the end of a maximal inspiration.

2 Vital capacity is the maximal volume of gas that can be *expelled* from the lungs by forceful effort following a maximal inspiration.

3 Inspiratory capacity (formerly complemental or complementary air) is the maximal volume of gas that can be inspired from the resting expiratory level

4. Functional residual capacity (formerly functional residual air, equilibrium capacity, or mid capacity) is the volume of gas remaining in the lungs at the resting expiratory level The resting *end expiratory* position is used here as a baseline because it varies less than the end-inspiratory position.

Normal values for lung volumes are given in Table 19 It may be seen that there are considerable variations in even healthy individuals. Therefore measured deviations from "normal" in a given patient must be relatively large to be significant. This accounts in part for the skeptical attitude with which many clinicians have come to



LUNG VOLUMES

Fig 189 Lung volumes It is important to consider how different types of intrathoracic disease—such as large mediastinal tumor, atelectasis, or chronic emphysema—may affect the static lung volumes (From COMROE, J H, JR, FORSTER, R E, II, DUBOIS, A B, BRISCOE, W A, AND CARLSEN, E *The Lung—Clinical Physiology and Pulmonary Function Tests* Chicago, Year Book Publishers, Inc, 1955)

regard lung function tests, in addition to the fact that in almost 8 out of 10 subjects the experienced clinician can estimate the respiratory function with sufficient accuracy on clinical grounds alone Even so, in the few subjects in whom an accurate assessment of lung function is of critical importance, lung function studies can be extremely valuable *Changes* in lung function from one month to another are informative, if sufficiently great

As with individual liver function tests, individual lung function tests and lung volumes need not always be abnormal in the presence of lung disease The various measurements of liver or of lung function often evaluate entirely different aspects of the total physiology of the respective organs

TABLE 19 NORMAL LUNG VOLUMES

	50 Young Men (Recumbent)		40 Young Women (Recumbent)		11 Men > 50-Yr † (Semirecumbent)	
	Mean	S.D	Mean	S.D	Mean	S.D
Age (years)	22 9	3 3	23 1	3 4	61 5	6 8
Height (cm)	176 2	5 1	163 4	4 2	169	4 8
Weight (kg)	72 5	11 2	57 2	9 4	65 9	12 4
Inspiratory capacity (liters)	3 79	0 52	2 42	0 36	2 61	0 61
Expiratory reserve volume (liters)	0 98	0 26	0 73	0 19	1 01	0 38
Vital capacity (liters)	4 78	0 59	3 14	0 41	3 48	0 48
Residual volume (liters)	1 19	0 35	1 10	0 30	2 43	0 50
Functional residual capacity (liters)	2 18	0 50	1 82	0 30	3 44	0 74
Total lung capacity (liters)	5 97	0 81	4 24	0 57	5 92	0 67
RV/TLC × 100 (%)	19 8	4 4	25 9	5 0	40 9	7 1

* From Kaltreider N L Fray W W and Hyde H V Z Am Rev Tuberc 37: 662 1938

† From Greifenstein F E King R M Latch S S and Comroe J H Jr Appl Physiol 4 641 1952

(From Comroe J H Forster R. E II Dubois A B Briscoe W A and Carlsen E *The Lung Clinical Physiology and Pulmonary Function Tests* Chicago Year Book Publishers Inc 1955)

For this reason the entire battery of tests may be required to assist in identifying the functional derangement that is present. For example, the vital capacity may be normal in the presence of considerable pulmonary disease which interferes with diffusion or pulmonary blood flow The vital capacity is reduced by pneumothorax, hydrothorax, pneumonia, or pulmonary edema to cite only a few

The *residual volume* and the *functional residual capacity* are important indices The residual volume obviously cannot be measured directly, but it can be measured indirectly One method is based upon the nitrogen that is flushed from the lungs while the subject is breathing pure oxygen the expired air is collected in a spirometer that has first been flushed with oxygen to remove nitrogen (for air contains 80 per cent nitrogen, Table 20) By measuring the nitrogen collected in the spirometer and using suitable calculations, the residual air can be computed An increase in the residual air is often taken to represent structural emphysematous changes but, more accurately it represents hyperinflation that may be due to (1) chronic emphysema, (2) partial obstruction of the airway, as in bronchostenosis, (3) overdistention of the remaining lung following resection of lung tissue, and (4) deformity of the thorax.[3]

TABLE 20 GAS COMPOSITION OF THE ATMOSPHERE

	Volume Per Cent		
	Inspired (atmospheric) air	Expired air	Alveolar air
Oxygen	20 94	16 3	14 2
Carbon dioxide	0 04	4 0	5 5
Nitrogen (including argon 0 94 per cent and other rare gases)	79 02	79 7	80 3

Lung Function Tests

The several lung volumes given in Table 19 and Figure 189 do not actually measure lung function. These volumes might all be relatively normal but due to inadvertent ligation of one main pulmonary artery at lobectomy, the function of the involved lung would be nil. Or diffusion across the alveoli to and from the pulmonary capillaries might be so impaired that despite relatively

MEAN VALUES FOR BLOOD O_2, CO_2 AND pH IN HEALTHY YOUNG MEN

	Arterial Blood	Mixed Venous Blood
1 O_2 pressure (mm Hg)	95	40
2 Dissolved O_2 (ml O_2/100 ml W B.)	0 29	0 12
3 O_2 content (ml O_2/100 ml W B)	20 3	15 5
4 O_2 combined with Hb (ml O_2/100 ml W B)	20 0	15 4
5 O_2 capacity of Hb (ml O_2/100 ml W B)	20 6	20 6
6 % saturation of Hb with O_2	97 1	75 0
7 Total CO_2 (ml CO_2/100 ml W B)	49 0	53 1
(mM/liter)	21 9	23 8
8 Plasma CO_2 (ml CO_2/100 ml plasma)	59 6	63 8
(a) Dissolved CO_2 (ml CO_2/100 ml)	2 84	3 2
(b) Combined CO_2 (ml CO_2/100 ml)	56 8	60 5
(c) Combined CO_2/dissolved CO_2	20/1	18 9/1
(d) CO_2 pressure (mm Hg)	41	46 5
9 Plasma pH	7 40	7 376

Fig 190 Blood gas values (From COMROE, J H, JR, FORSTER, R E, II, DUBOIS, A B, BRISCOE, W A, AND CARLSEN, E *The Lung—Clinical Physiology and Pulmonary Function Tests* Chicago, Year Book Publishers, Inc, 1955)

normal lung volumes and pulmonary blood flow, respiratory efficiency could be markedly impaired It is therefore apparent that efficient lung function requires the efficient operation of three major functional elements. (1) pulmonary ventilation, (2) alveolar-capillary membrane gas transfer, and (3) pulmonary blood flow

The primary requirement of lung function is the oxygenation of, and the removal of carbon dioxide from, venous blood The venous blood in the pulmonary artery has a relatively low oxygen content but an elevated carbon dioxide content (for average normal values, see Fig 190) This cyanotic blood normally passes through the pulmonary capillary bed that is surrounded by well ventilated alveoli, and pink blood whose hemoglobin is largely saturated with oxygen and largely cleared of carbon dioxide then enters the pulmonary veins to return to the left atrium Obviously, since cellular oxygenation is an ultimate goal of "respiration," the efficiency of the systemic circulation in transporting the oxygenated blood to the peripheral tissues—as well as the efficiency with which the peripheral tissues utilize the oxygen—are also important elements in the total respiratory process That is, oligemic shock can produce cellular anoxia very quickly even in the presence of normal lung function

For emphasis, then, let it be clearly understood that lung function can be reduced by a defect in either *ventilation, diffusion,* or *blood flow,* or by any combination of these First, diminished breathing reduces ventilation, as may atelectasis, or intrapulmonary gas mixing may be uneven, as in emphysema Second, the diffusion surface area may be reduced, as in emphysema or by pneumonectomy, the diffusion efficiency of a normal total diffusion surface area may be reduced in interstitial edema or fibrous thickening of the alveolar walls (Fig 191) Third, abnormal pulmonary blood flow, as through a large pulmonary arteriovenous fistula (Figs 174 and 192), may result in cyanosis because of the fact that a large amount of unsaturated pulmonary arterial blood bypasses the pulmonary capillary bed and enters the pulmonary veins directly, here pulmonary ventilation and alveolar diffusion may be normal As another example of the interplay of blood flow and ventilation (Fig 193), let it be assumed that the blood flow to a portion of the lung is adequate but that this portion of the lung

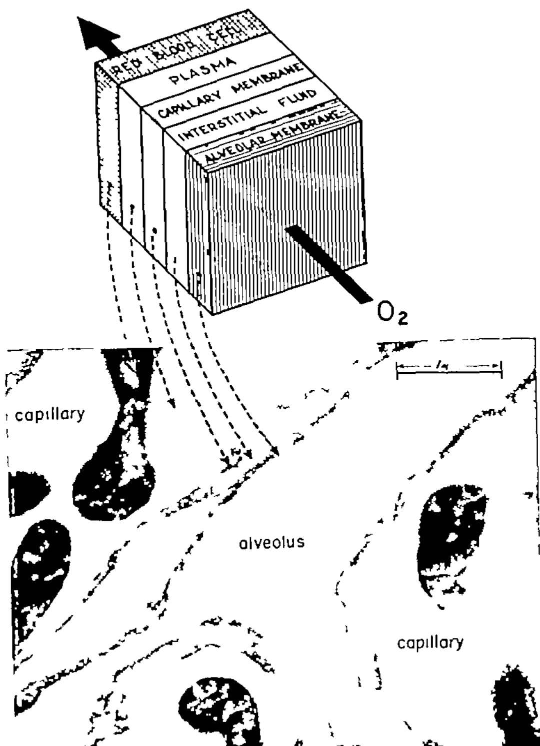


Fig 191 Electron microscope photograph of rat lung, showing the layers through which the blood gases must pass. It is difficult to separate diffusion defects from defects due to impaired pulmonary ventilation and blood flow However *diffusion* abnormalities do exist in many patients (*e.g.*, pulmonary edema in mitral stenosis, hyaline membrane disease) and this important element in respiration becomes of increasing concern as problems in *ventilation* and *pulmonary blood flow* are better understood. (From Comroe, J H., Forster, R E II Dubois A B Briscoe, W A and Carlsen E. *The Lung—Clinical Physiology and Pulmonary Function Tests*. Chicago Year Book Publishers, Inc., 1955)

is not adequately ventilated such as may occur in the presence of lobar pneumonia the blood passing through this portion of the lung will not be oxygenated and upon entering the main blood stream, it will impart the appearance of cyanosis This is sometimes referred to as a functional arteriovenous shunt, in contradistinction to the

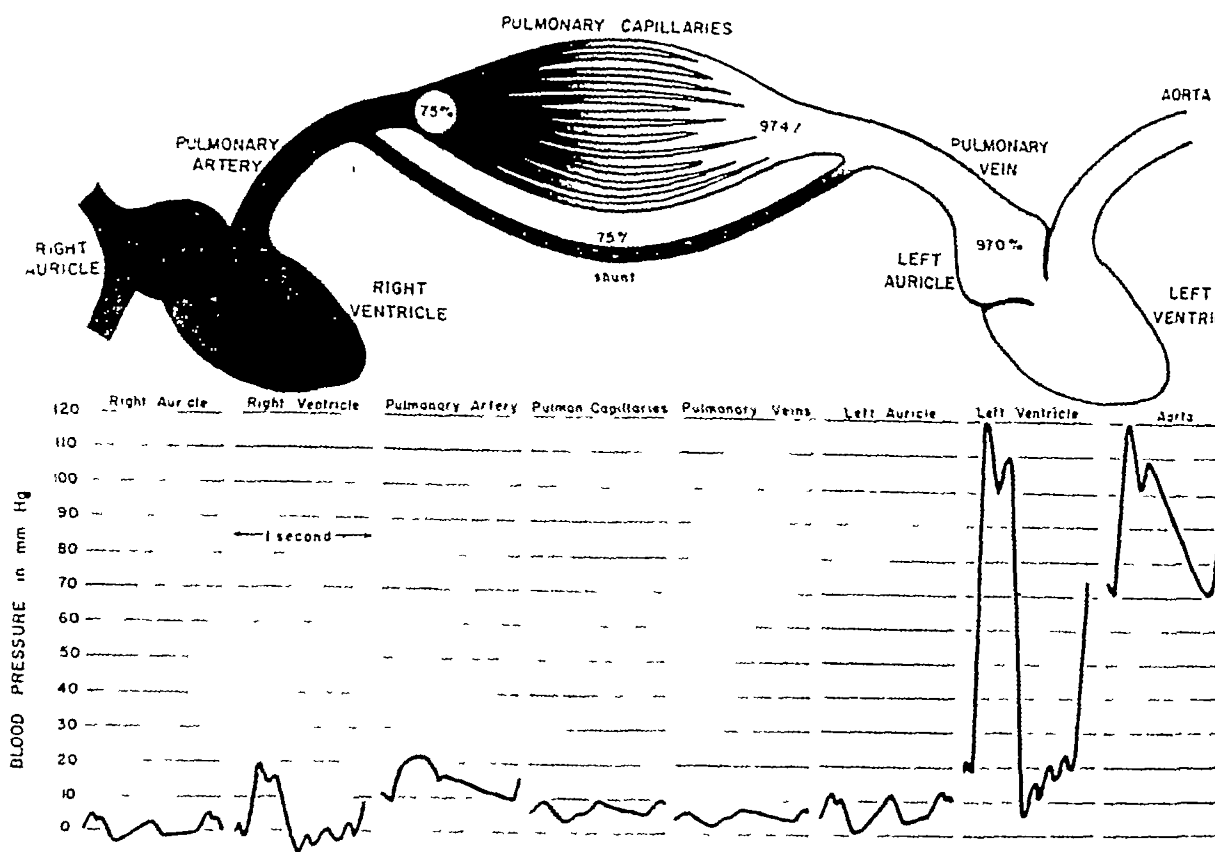


Fig 192 The pulmonary circulation The great disparity between right ventricular and left ventricular pressure is apparent Much less force is required to propel blood through the lungs than through systemic areas supplied by aortic blood (From COMROE, J H, JR, FORSTER, R E, II, DUBOIS, A B, BRISCOE, W A, AND CARLSEN, E *The Lung—Clinical Physiology and Pulmonary Function Tests* Chicago, Year Book Publishers, Inc, 1955)

true anatomic pulmonary arteriovenous shunt or fistula Of course, a right to left intracardiac shunt will also produce cyanosis, and cyanosis alone does not indicate whether the pathology is in the lungs or in the heart

Now that the several components of respiratory function have been outlined, let us consider measurements which reflect the efficiency of the total process

Arterial oxygen content [7] Since the major function of the lung is to arterialize the venous blood (that is, to add oxygen and to remove excess carbon dioxide) it is patently of value to analyze the gas content of arterial blood at rest and during exercise If the arterial gas values are abnormal at rest or become abnormal on exercising, further studies may then be performed to identify where the fault lies, if it is not clinically apparent

The measurement of the venous oxygen concentration is of no practical aid in e mating the efficiency of pulmonary funct since the venous oxygen saturation will pend upon the amount of oxygen whic removed in the peripheral tissues, whic turn will depend upon the metabolic r The concentration will also depend u the speed of the circulation, since the gre the volume of blood that passes throug given tissue, the less the amount of oxy that will be removed from any partic 100 cc of blood Of course, the degree venous oxygen saturation is also influen by the arterial oxygen saturation of blood which was transported periphera Finally, by immersing the hands in water the rate of blood flow can be so creased that the gas values in venous bl leaving the hands closely approach those arterial blood

Arterial oxygen content may be expres on the basis of percentage hemoglobin sat

ration, volumes per cent, or as oxygen tension (mm. Hg) The last reflects more precisely relatively small changes in arterial oxygen content. The normal oxygen content of arterial blood is from 19 to 21 vol per cent. The normal arterial oxygen saturation is from 96 to 99 per cent, and the normal arterial oxygen tension ranges from 90 to 102 mm Hg The normal pH of arterial blood ranges from 7.38 to 7 42

A low *arterial oxygen saturation* (the measurement of arterial oxygen saturation is more readily carried out than is the measurement of arterial oxygen tension) does not necessarily mean that pulmonary disease is present since, as was pointed out, an intracardiac right to left shunt (Fig. 155) or a pulmonary A V fistula (Fig. 192) may result in cyanosis due to reduced arterial oxygen saturation. Nevertheless, a low arterial oxygen saturation may, and commonly does, indicate pulmonary disease and further studies are indicated.

Pulmonary insufficiency versus pulmonary disability It is useful here to make the distinction between pulmonary insufficiency and pulmonary disability the former may result in inadequate oxygenation of the blood with cyanosis but the person may carry on his usual activities on the other hand, in certain diseases the arterial oxygen saturation may be normal, but it is maintained at a normal level through such severe respiratory effort that the individual has pulmonary disability even though he may not yet have pulmonary insufficiency That is *pulmonary disability is related to the amount of physical effort that must be expended to provide whatever pulmonary function is achieved* For example the asthmatic patient may by sufficient effort succeed in maintaining adequate alveolar gas exchange and a normal arterial oxygen saturation but the effort required to maintain normal blood gas levels is such that the resulting dyspnea quite incapacitates the individual.

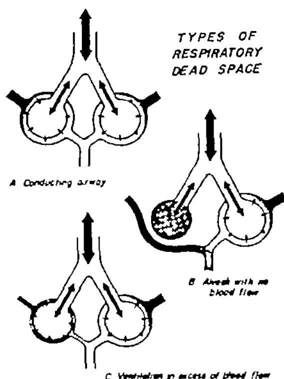


Fig 193 Dead space is here used to indicate bronchopulmonary space which contains air that is of no assistance in total respiration Obviously the air that remains in the trachea and bronchi does not assist in oxygenating the blood or in removing CO_2 (*A*) Similarly if a ventilated alveolus has no blood flow effective respiration in this unit is impossible (*B*) Finally the alveolar ventilation may be in excess of blood flow (*C*) A non ventilated alveolus that is still perfused with blood constitutes a functional shunt in contradistinction to a true pulmonary arteriovenous (A V) shunt (Fig. 192) (From Comroe, J H., Jr., Forster, R E., II Dubois A B Briscoe, W A and Carlsen E *The Lung—Clinical Physiology and Pulmonary Function Tests* Chicago Year Book Publishers Inc 1955)

The arterial oxygen saturation will not give evidence of even very large pulmonary lesions unless these lesions are not being aerated while still being perfused with blood Even a pneumonectomy is followed by a normal arterial oxygen saturation in most instances especially if the patient is at rest In contrast cyanosis may be present (diminished arterial oxygen saturation) when both lungs are *in situ* if a lobe or a lung is defective and not being ventilated while still being perfused with blood such as might occur in atelectasis or in lobar pneumonia.

Whereas even severe exercise does not usually produce cyanosis in a normal sub

ject, exercise may decrease arterial oxygen saturation in the presence of right to left shunts (intracardiac or intrapulmonic), in "functional" shunts, in patients with a sharp reduction in diffusion surface area, and in subjects who cannot adequately increase pulmonary ventilation in proportion to the demands of the exercise In the absence of intrapulmonary or intracardiac anatomic vascular shunts, a decrease in arterial oxygen saturation during exercise may be taken to indicate significant pulmonary disease

Arterial carbon dioxide content The arterial carbon dioxide content can be of considerable diagnostic importance, both as regards pulmonary function *per se* and in classifying states of acid-base imbalance The normal values are given in Figure 190 As was noted in the discussion of acid-base balance (p 40), an elevation of the total carbon dioxide content of arterial plasma may reflect either pulmonary insufficiency

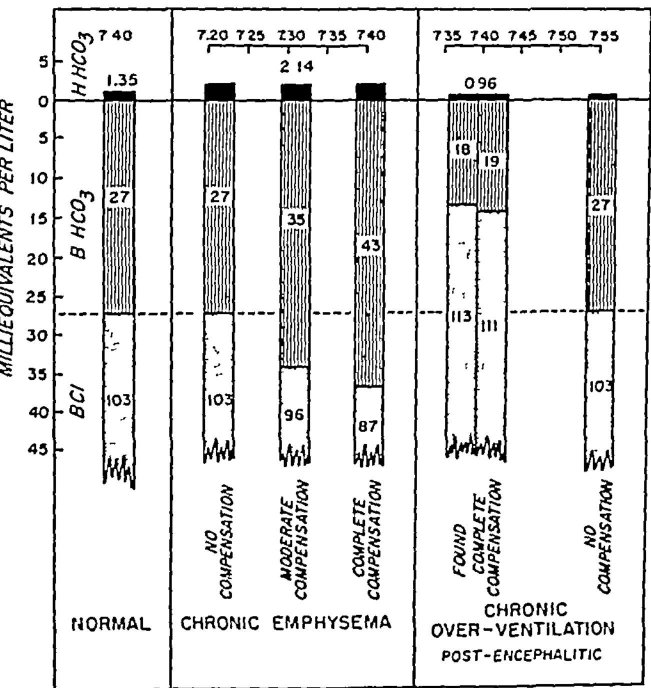


Fig 194 Respiratory acidosis in emphysema (including compensatory adjustments) and respiratory alkalosis in hyperventilation (including compensatory adjustments) Acidosis due to CO_2 retention is compensated for by chloride excretion and base-bicarbonate increase Alkalosis due to excessive CO_2 excretion is compensated for by chloride retention and base-bicarbonate reduction (Redrawn from Gamble, J L *Chemical Anatomy, Physiology, and Pathology of Extracellular Fluid* Cambridge, Mass, Harvard University Press, 1917)

for the elimination of carbon dioxide (respiratory acidosis), or it may reflect metabolic alkalosis due to the loss of chloride with a compensatory retention of carbon dioxide in the form of bicarbonate, combined largely with sodium To resolve the question the blood pH may be used, for in respiratory acidosis the value will be depressed and in metabolic alkalosis it will be increased—assuming that in neither case is compensation complete Therefore, if the blood pH is decreased below normal in the presence of an elevated carbon dioxide tension and content, it indicates that the lungs are no longer capable of eliminating carbon dioxide with sufficient rapidity to prevent respiratory acidosis Such may develop because of inadequate pulmonary ventilation during anesthesia, because of exhausted soda lime in the rebreathing system, or because of pulmonary emphysema Conversely, the total arterial carbon dioxide content may be diminished in either respiratory alkalosis (hyperventilation syndrome) (Fig 194) or metabolic acidosis (Fig 26) Here again, the measurement of the blood pH is helpful in distinguishing between the two conditions, though the clinical features of the case will usually render accurate interpretation possible without recourse to blood pH measurements, which may not be available

Except in unusual instances—such as during closed anesthesia where the carbon dioxide is ineffectively removed due to inadequate ventilation, while oxygen is administered in increased concentrations under positive pressure—an increase in carbon dioxide content of the blood resulting from pulmonary insufficiency is virtually always associated with anoxemia That is, an insufficiency for carbon dioxide elimination is usually accompanied by an insufficiency for oxygen uptake On the other hand, anoxemia can readily occur without the retention of carbon dioxide This is because the elimination of carbon dioxide across the capillary membrane proceeds with much greater facility and speed than does the

uptake of oxygen. Poorly ventilated alveoli result in the blood's leaving the alveoli with an elevated carbon dioxide content and a low oxygen content. Hyperventilated alveoli, on the other hand (Fig. 193), can do no more than saturate the blood with oxygen, whereas they can effect a greater than usual decrease in the blood carbon dioxide concentration As the blood from poorly ventilated areas mixes with the blood from hyperventilated areas in the pulmonary veins, the unsaturated blood reduces the average arterial oxygen saturation, in contrast the blood with the increased amounts of carbon dioxide mixes with blood from which an unusual amount of carbon dioxide has been removed, resulting in a normal carbon dioxide content or perhaps even a reduced carbon dioxide content.

A low arterial CO_2 tension that is associated with a low O_2 tension may reflect a diffusion problem

It may be seen, therefore, that the carbon dioxide content of arterial blood may be elevated, normal, or low in patients with pulmonary disease A normal or even a low level does not necessarily indicate that pulmonary disease may not be present but it does indicate that the individual is still able to eliminate carbon dioxide satisfactorily If this elimination of carbon dioxide is achieved at the expense of disabling respiratory effort, though then pulmonary sufficiency for the elimination of carbon dioxide has been maintained at the expense of pulmonary disability

The comparison of the arterial oxygen saturation and carbon dioxide content during the breathing of air and then of pure oxygen can be utilized to give information regarding the over all ability of the lung to perform its mission of saturating the blood with oxygen and eliminating carbon dioxide. Exercise imposes additional stress on this mission and shunts may thus be demonstrated

ADDITIONAL INDICES OF LUNG FUNCTION

Tidal volume. As stated tidal volume normally ranges from 500 to 600 cc. per respiratory exchange. However, all of this expired air does not reach the ultimate destination, the alveoli, since a portion of it remains in the *dead space* consisting of the nose, mouth, pharynx, trachea, and bronchi (Fig. 184) Fowler[5] estimated the dead space at approximately 150 cc for males and 110 cc for females If the tidal volume is 500 cc and the respiratory dead space in the particular individual in question is 150 cc, then only 350 cc of the inspired air actually reaches the alveoli to participate in the exchange of oxygen and carbon dioxide Obviously, the individual who is taking shallow respirations reduces the margin between the total volume of the inspired air and the dead space, with a consequent diminution in alveolar ventilation.

Minute volume The minute volume is the product of the tidal volume and the respiratory rate If the tidal volume is 500 cc per respiratory cycle and the patient breathes 20 times per minute, the minute volume will be 20 × 500 or 10 L If the dead space is equal to 150 cc of each tidal volume, then the volume of alveolar ventilation would be 10 L minus 3 L., or 7 L. On the other hand, if the tidal volume were 1 L and the rate of respiration 10 per minute, the minute volume would be 10 L per minute and the effective alveolar ventilation would be 8.5 L per minute Thus, the dead space is of importance in both normal and abnormal respiration, and we shall find that it further aggravates the pathophysiology of flail chest and sucking wounds of the thorax

Vital capacity further comment It was seen that the vital capacity is the maximum amount of air that can be expelled following the deepest possible inspiration It varies with age, physical build, and sex and is usually greater in males. It normally ranges from about 3500 to almost 6000 cc, and it is by all odds the most commonly used single test of pulmonary function. If the individual can and does cooperate, then a significant diminution in the vital capacity has clinical significance. Many disease con-

ditions may cause a reduction in the vital capacity, among these are atelectasis (Figs. 180 and 181), bronchial obstruction (Fig 180), pulmonary fibrosis (Fig 207), pulmonary edema (Fig 149), lung cyst (Figs 203 and 204), pleural effusion (Figs 183 and 208), tumors (Fig 202), lung resection, and pneumonia Nevertheless, a diminished vital capacity does not necessarily mean that parenchymal lung disease is present, since phrenic nerve paralysis or pleural effusion may also reduce the value Even so, a normal capacity is reassuring as regards total lung volume, whereas a marked reduction in the vital capacity certainly indicates that the patient must be studied carefully before pulmonary surgery is attempted The timed vital capacity can be abnormal when the untimed value is normal, as in emphysema

The precise value obtained for the vital capacity varies considerably in different normal subjects, and strongly indicated pulmonary surgery should not be omitted merely because the vital capacity is relatively low If the vital capacity is only 2 L but pulmonary function is otherwise generally fair, operation to resect residual tuberculous foci may still be performed, particularly if the portion of lung to be excised is not assisting in respiration Actually, the diseased lobe or segment may not be ventilated but may still be perfused with blood, thus interfering with respiration by serving as a functional shunt (Fig 188)

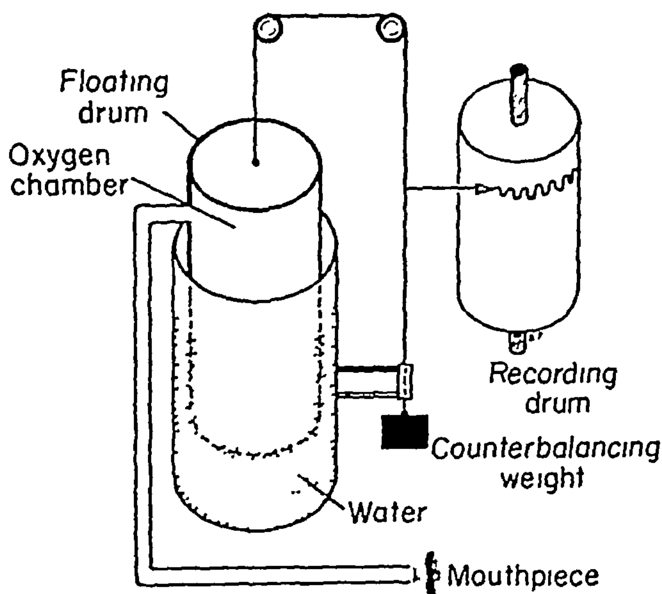


Fig 195 The spirometer and associated apparatus are used to measure various of the lung volumes and capacities The respiratory excursions are recorded on the drum which revolves at constant speed By simple calculations the volume of gas moved with each respiration or with a series of respirations over a timed interval can be estimated

It has, again, been noted that the vital capacity may be normal in the presence of extensive pulmonary disease that does not diminish the intrathoracic space, as in emphysema Therefore, while the vital capacity is an important single measurement of pulmonary status, it alone does not reflect adequately the efficiency of pulmonary reserve Other indices are required

Maximum breathing capacity This volume is the maximal volume that can be breathed in 1 minute by the greatest possible voluntary exertion After one practice or trial effort to allow the subject to determine what tidal volume he will use and what rate of respiration he will employ, he is asked to breathe as deeply and as rapidly as he can through a low resistance system (Fig 195) for 15 seconds The individual will ordinarily employ only that portion of the vital capacity which is in the intermediate range, since the extremes of the vital capacity require an undue amount of time and effort (Figs 196 and 197) The normal range of the maximum breathing capacity is from about 80 to 120 L/min, women having a smaller maximum breathing capacity than men Individual variations in the maximum breathing capacity are large, and the variation from the anticipated normal must be great to be significant

The maximum breathing capacity is not necessarily closely correlated with the vital capacity, for usually the individual will use only a part of the vital capacity in performing the maximum breathing capacity measurement (Fig 197) Actually, the normal individual will ordinarily use a tidal volume of about 50 per cent of the vital capacity, and the rate will vary considerably from about 50 to 70 respirations per minute

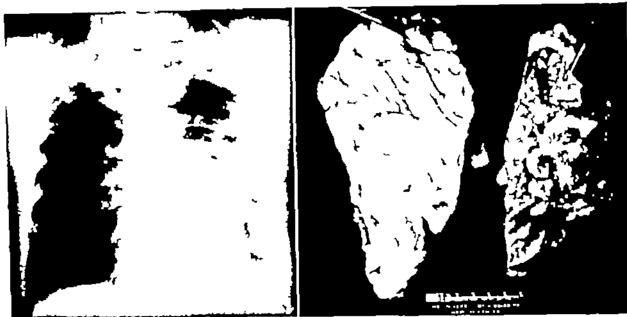


Fig 196 Decortication for chronic empyema. *Left* Left empyema cavity without definite fluid level. *Right* Greatly thickened and fibrous pleural "peel" removed Not only the lung itself but also the adjacent chest wall may be mobilized by decortication in such cases (see Fig. 197)

It follows that the person with a limited vital capacity but with an ability to breathe rapidly may have as good a maximum breathing capacity as the person who has a normal vital capacity, since both are using only about one half the vital capacity Thus, the maximum breathing capacity may be normal in instances where the vital capacity is reduced, or, the maximum breathing capacity may be reduced where the vital capacity is normal.

Obstruction of the bronchi or loss of elasticity of the lungs are potent factors in diminishing the maximum breathing capacity conditions which are prominent in emphysema, the emphysematous patient who may have a normal vital capacity generally has a significantly reduced maximum breathing capacity On the other hand the patient with pulmonary fibrosis may have a maximum breathing capacity that is normal (Fig. 198) but have a low total vital capacity Again this is due to the fact that the individual with pulmonary fibrosis can breathe rapidly and since in the maximum breathing capacity test only a portion of the normal vital capacity is employed he may produce the same volume of air exchange per minute as a normal individual.

It is important to comprehend the relationships which exist between total vital capacity and timed vital capacity in such different conditions as emphysema, pulmonary fibrosis, and restrictive disease such as chronic empyema.

Exercise tolerance In clinical practice, one of the very best measurements of pulmonary functional reserve is the presence or absence of dyspnea on walking the length of a hallway or in climbing 1 or 2 flights of stairs If the individual is not unduly dyspneic on moderate exercise (and, of course if he has not been dyspneic at rest), then he will usually withstand satisfactorily the removal of diseased, relatively functionless lung tissue, within reason Naturally, the greater the amount of pulmonary tissue to be resected, the greater the care with which pulmonary function must be assessed Ideally, one may use standardized tests such as walking on a treadmill pedaling a stationary bicycle, or repeated mounting and descending from a platform, but ordinary exercise provides a practical compromise

Bronchospirometry Bronchospirometry is the term applied to the selective measurement of the ventilatory capacity through a single main stem bronchus. With the aid of an appropriate tube which excludes the

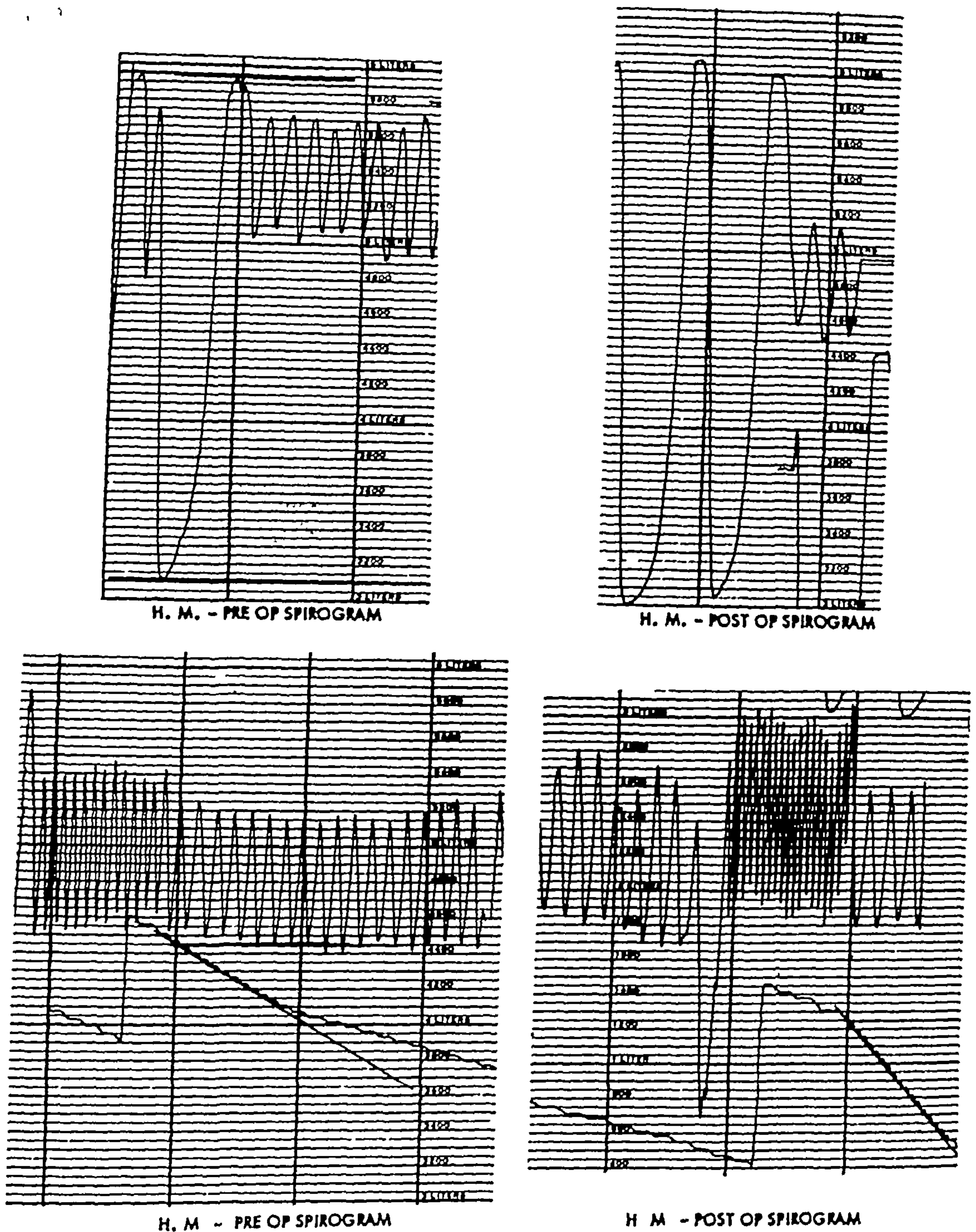


Fig 197 Spirograms of a patient with empyema before and following pulmonary decortication (see Fig 196) In the two spirograms shown *above it may* be seen that the *timed vital capacity* was not changed much by decortication However, below it is seen that the *maximal breathing capacity* was considerably improved by operation, as reflected by the much sharper angle of ascent of the straight line summating volume The improvement in ventilation was considered to be the result of lessened fixation of the thoracic cage on the involved side (Courtesy of Dr Josef R Smith)

air from the other main stem bronchus, the actual ventilation from one lung can be measured This has the obvious advantage of affording evidence regarding the relative contribution of each lung in the total respiratory effort For example, it may be found that one lung is providing a very small percentage of the total ventilatory effort and that therefore the removal of this lung will not seriously further diminish the respiratory function of the individual The oxygen consumption and the CO_2 excreted by each lung is also measured The right lung usually contributes approximately 55 per cent of the vital capacity and absorbs 55 per cent of the oxygen, the left lung 45

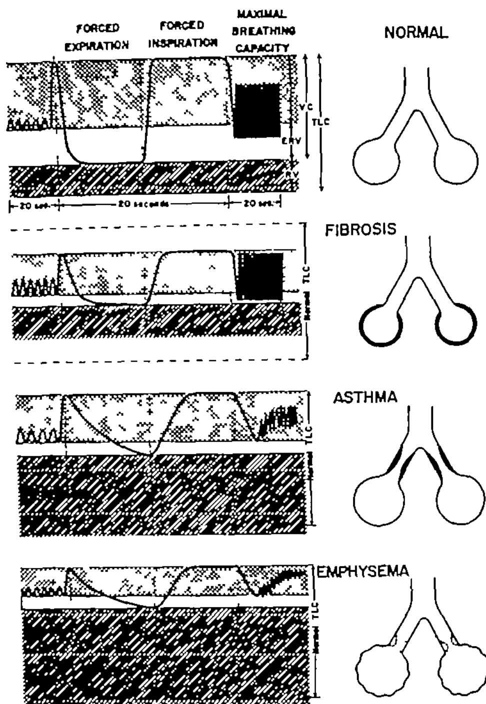


Fig 198 Pulmonary fibrosis The residual volume is not greatly altered but the expiratory reserve volume and the total lung capacity are reduced

Asthma There is evidence of air trapping, the timed vital capacity would suggest bronchostenosis or spasm the expiratory reserve volume is much reduced and the residual volume is much increased

Emphysema. The spirograms exhibit a diminished timed vital capacity there is air trapping due to bronchospasm and stenosis the expiratory reserve volume is much diminished the residual volume is greatly increased. Pulmonary disability and pulmonary insufficiency are both likely to exist. (From Comroe, J H., Jr., Forster, R. E., II Dubois A B Briscoe, W A., and Carlsen E *The Lung—Clinical Physiology and Pulmonary Function Tests.* Chicago Year Book Publishers, Inc., 1955)

per cent. Moreover, on the basis of oxygen uptake and ventilation, values for the relative volumes of blood flow can be estimated

While theoretically information obtained by bronchospirometry should be ideal, in clinical practice the use of this technic has not been very satisfactory, in our experience. The actual performance of broncho-

spirometry is more difficult than the uninitiated might imagine, for it requires earnest cooperation on the part of several individuals, one being the patient The breathing through the tube is always stenotic breathing (and therefore abnormal), and this makes the accurate interpretation of the spirographic tracings difficult Moreover, in the critically ill individual where the information would be of the most value, the patient frequently cannot tolerate the asphyxiating effect of introducing the tube This is particularly true in patients who have not only a diminished pulmonary reserve but who have also abundant pulmonary secretions (tuberculosis, bronchiectasis) The struggles which result from the tube's being placed may largely invalidate the results in most patients

X-rays and fluoroscopic examination Much information regarding the probable vital capacity can be ascertained from the chest roentgenograms and from fluoroscopic observation of the leaves of the diaphragm during respiration In the patient with emphysema the leaves of the diaphragm are flat, and the diaphragmatic movement with each respiratory cycle is minimal Such individuals usually have a diminished ventilatory capacity In fact, a radiologist who is especially interested in lung function can often predict with much accuracy the values that will be obtained in measuring certain indices of lung function

Breathing reserve The breathing reserve is defined as the difference between the maximum breathing capacity and minute volume of breathing For example, if the maximum breathing capacity is 100 L per minute and the minute volume is 10 L per minute, the breathing reserve is 90 L per minute When this individual exercises vigorously, on the other hand, his minute volume may rise to 70 L and thus his breathing reserve is reduced to 30 L (100 L minus 70 L) It is clear that the breathing reserve may be reduced either because of a decrease in maximum breathing capacity or an increase in minute volume of breathing More frequently it is due to the former According to Comroe and his associates,[2] the minute volume of resting patients with pulmonary disease rarely exceeds 20 L per minute The minute volume of breathing at which a patient experiences dyspnea is a useful value clinically

Spirograms The use of spirograms has been implicit in the foregoing discussion Tracings may be made of normal breathing, vital capacity, and maximum breathing capacity upon a rapidly moving drum These provide a permanent record for comparison with later tracings, and they also permit analysis of many characteristics of the breathing pattern Among the data so derived are the following (1) The actual and relative periods required for normal inspiration and expiration [Ordinarily expiration requires 1 2 times as long as inspiration, but in the presence of expiratory obstruction (asthma, emphysema) and where the elastic fibers of the lungs are diminished, the expiratory time may be prolonged] (2) The speed of normal and maximal inspiration and expiration Normally, the air flow is rapid and results in deep inspiratory and expiratory slopes, with the exception of the terminal portion (Fig 185) In emphysema, however, although the vital capacity may be normal the rate of air flow is slowed throughout—particularly through the latter one-half of expiration, that is, the *timed* vital capacity would be reduced Cournand and Richards[4] found that in congestive heart failure the flow was slower for the last few hundred cubic centimeters of *both* inspiration and expiration (3) Interval for the chest to return to the resting expiratory level, when allowed to return passively to the expiratory position following maximal inspiration Normally, all the inspired air will be expelled before the next inspiration, but in patients with emphysema or bronchial obstruction this is not so

Intrapulmonary gas distribution (mixing) Even though the actual ventilation volume of the lungs (from the point of view

empyema Later on, as it became possible to perform pneumonectomy without the almost routine development of infection in that hemithorax, there arose concern regarding what the ultimate effect of overdistention of the remaining lung would have upon its function, since overdistention of varying degrees did exist where thoracoplasty was not done.

Actually, doubt still exists regarding whether or not thoracoplasty should be routinely done following pneumonectomy (we do not in the routine case), but it is unquestionably true that marked overdistention with emphysema does have certain untoward effects upon the structure and function of the remaining lung This has been demonstrated with lung function tests

Yet, in some patients thoracoplasty on one side following pneumonectomy has been shown to have a deleterious effect on the mechanics of ventilation on the opposite side

THE NUMBER OF PULMONARY LOBES REQUIRED FOR SURVIVAL As many as 3 of the 5 lobes of the lungs have been excised with "adequate" pulmonary function remaining Overholt[16] reported 4 patients who had had all but 5½, 6, 7, and 8 segments removed, respectively These patients had an increased residual volume, a finding considered to be consistent with overdistention and more likely due to hyperinflation than to true emphysema

THE "PULMONARY CRIPPLE" In choosing between lobectomy and pneumonectomy for carcinoma of the lung, one will be influenced by the pulmonary function The improvement in "cures" by pneumonectomy does not justify an almost deliberate risk of pulmonary insufficiency, where pneumonectomy is performed in the face of markedly diminished pulmonary reserve, in our opinion Here lobectomy would be preferable

Indications and Value of Pulmonary Decortication

As an outgrowth of the experiences during the World War II, it was appreciated that the clot or "peel" which was formed by the deposition of fibrinous exudate and bl
over the surface of the lung could be
moved and the lung freed almost enti
in many instances (Fig 196) This pro
dure, termed decortication, is now routin
practiced, when indicated It is most f
quently required where the blood of a tr
matic hemothorax has been allowed to c
and thus it is advisable to keep the he
thorax as free of blood as possible by beg
ning aspiration as soon as the patient is se
If clotting does occur, streptokinase a
streptodornase may be employed promp
to liquefy the clot and permit aspiration
the fluid The use of such aggressive co
servative therapy early may often obvi
the need for subsequent thoracotomy a
decortication Chronic empyema may a
imprison the lung

At operation the constricting layer m
consist of only fibrinous exudate which
just beginning to organize and may be qu
thin On the other hand, the capsule or s
may be extremely leathery and fibrotic, a
at times it is extensively calcified The co
figuration of the sac, which covers not o
the visceral pleura but also the pariet
pleura, and which may contain fluid with
its cavity, can be visualized by thinking o
collapsed football that has been inserted in
the hemithorax and molded over the surfa
of the lung

Obviously a dense fibrous material ca
prevent the lung from reexpanding, but
is often surprising how thin a fibrinous lay
can be and still prevent effective expansi
of the lung The pressures which induce lu
expansion are indeed delicate ones

The degree of reexpansion and improv
ment which follows decortication varies co
siderably from one patient to anothe
Therefore, if almost complete reexpansio
has been achieved already, surgery wi
probably gain little or no additional fun
tion

Abnormalities of the Pulmonary Circula tion: Further Comment.

To review, the pulmonary circulation di
fers in certain fundamental aspects from th

systemic circulation. Among the more important of these are the following. First, the pulmonary arteries carry venous blood, whereas the pulmonary veins carry arterial blood to the left atrium in the normal heart. When one is operating upon the lung, a sudden gush of bright blood generally indicates venous bleeding; cyanotic or dark blood indicates arterial bleeding. Second, normally the pressure in the pulmonary artery is only about one-sixth the pressure in the systemic arteries and direct compression will usually control pulmonary hemorrhage. The systolic pressure in the pulmonary artery should be somewhat less than 20 mm. Hg, whereas the systolic pressure in the aorta might be on the order of 120 mm. Hg. The diastolic pressure in the pulmonary artery is, of course, considerably lower than the systolic pressure (Fig. 127). The development of pulmonary arterial hypertension may so increase the work of the right heart as to produce failure, for rarely the pulmonic pressure may equal systemic pressure. Third, the pulmonary arterial blood supply is not essential for nutrition of the lung itself; this requirement can be performed entirely by the bronchial arteries. That is, one can ligate the pulmonary artery to a lung with impunity so far as lung tissue viability is concerned, but he cannot ligate all bronchial arteries with impunity. Even here, however, there is some cross supplementation, in that it has been shown that whereas the bronchial arteries are necessary for adequate nourishment of the bronchus near the hilum, the pulmonary artery blood may nourish the more distal bronchi.

Blades and his associates[1] studied the effect of occlusion of all pulmonary vessels, including the bronchial arteries, for varying periods of time in dogs. They concluded that temporary occlusion of the vessels to one lung produced astonishingly little gross or microscopic change in pulmonary tissue. They felt that this might be of value in the production of a bloodless field for certain types of pulmonary surgery, including lung homotransplantation, and might also provide useful information in the maintenance of extracorporeal circulation. The important point was, however, that dogs in whom the ischemia to the lung had been maintained for as long as 360 minutes showed, at autopsy from 7 to 34 days later, no characteristic differences between the ischemic lung and the control lung in the given animal. Moreover, wound healing of incisions in the lung appeared to be progressing satisfactorily and normally when animals were sacrificed 14 days after the incision had been made in the ischemic lung.

In a somewhat different study, Wyatt, Burke, and Hanlon[23] studied the morphologic effects upon canine lungs of ligation of the pulmonary veins. The pulmonary veins from the right or left lung were divided in 25 dogs. Division of the left pulmonary veins did not result in death but, in contrast, the mortality was high when the right pulmonary veins were divided, though this mortality was obviated by the postoperative administration of penicillin. It was considered possible that the greater severity of reaction following ligation of the right pulmonary veins could have been due to quantitative differences in venous flow on the two sides, since the circulation through the right lung is considered to represent approximately three-fifths of the total pulmonary circulation, as against two fifths through the left lung. In contrast to circumstances in which the pulmonary artery had been ligated, Wyatt and his co-workers found that interruption of the venous drainage from the lung resulted in intense and diffuse capillary congestion and extravasation into the lung. Nevertheless, anatomic study of lungs following ligation of the veins revealed rapid clearance of the blood constituents within 6 weeks without evidence of infarction. At the end of 12 months there was complete expansion of the lung. During this time hypertrophy of the bronchial veins may have occurred to shunt blood to the systemic venous system and thus relieve pulmonary congestion. The bronchial veins which chiefly drain the hilar bronchi and major subdivisions deliver their blood into the azygos, hemiazygos, and intercostal veins. These

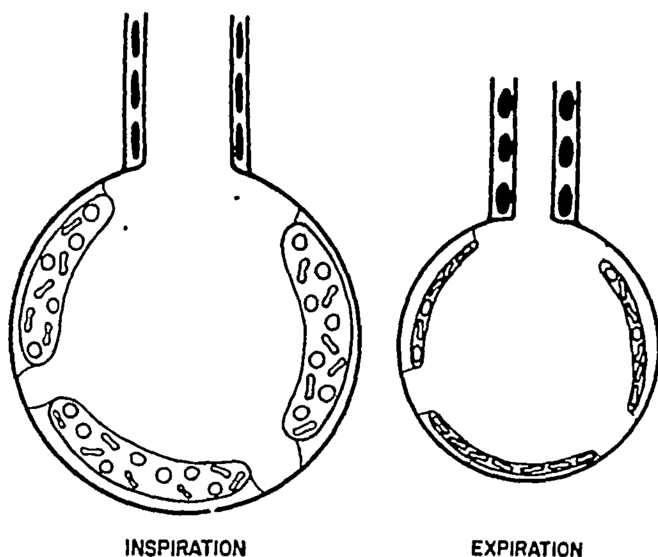


Fig 199 Schema to illustrate the effect of respiration on the pulmonary circulation The alveolus in inspiration is shown with large volume Its contained air is indicated by the widely separated dots representing relative rarefaction due to the diminished intra-alveolar pressure The bronchiole is widely dilated, permitting free access of air into the alveolar chamber The reduced intra-alveolar pressure permits engorgement of the pulmonary capillaries shown filled with red blood cells The alveolus in expiration is smaller due to the diminished air volume The bronchiole is constricted, increasing the resistance to outflow of air The increased air pressure in the alveolus (suggested by the greater concentration of dots) acts to compress the capillaries and thus increases the resistance to flow through these vessels (From RODBARD, S Bronchomotor tone—a neglected factor in the regulation of the pulmonary circulation Am J Med, **15**. 356, 1953)

vessels may be enormously dilated in the bronchial mucosa of a patient with pulmonary hypertension The bronchial veins may therefore serve as collateral flow to return blood by way of the caval system to the right atrium rather than by way of the pulmonary veins to the left atrium It has been shown that there is a cross communication between pulmonary arterial and bronchial venous flow In addition to this collateral flow, innumerable pleural adhesions may provide escape of pulmonary arterial blood from the lungs in some patients with pulmonary hypertension

At pulmonary resection it is preferable, as stated, to ligate the pulmonary artery first and ligate the vein second The reason for this is that in doing a pneumonectomy, to ligate the vein first will lead to the entrapment of a considerable volume of blood within the lung before the pulmonary artery is occluded In contrast, ligation of the pulmonary artery first allows blood to drain from the lung, and one thus does not remove as much blood with the excised lung Furthermore, the lung that is not congested with blood is far more easily retracted and maneuvered about in the chest to gain exposure than is the congested or the emphysematous lung Finally, ligation of the pulmonary artery first does not irrevocably commit one to resection, for gangrene will not occur, however, to ligate the pulmonary veins is to risk lung gangrene Of course, this feature of congestion following initial ligation of the veins takes on decreasing significance as one goes from pneumonectomy, to lobectomy, to segmental resection In the last there is no particular preference as to which vessel is ligated initially, though the artery is usually taken first

BRONCHOMOTOR TONE RÔLE IN REGULATION OF PULMONARY CIRCULATION Rodbard[10] reviewed current theories regarding the effects of bronchomotor tone on the pulmonary circulation The *arteriolar concept* holds that the arterioles of the lung are essentially similar to those of the systemic circulation and that muscular contractions in the walls of these vessels largely regulate circulation through the lungs Yet, a well established musculature in the walls of these vessels has never been clearly demonstrated, in contrast, there is abundant musculature in the walls of the bronchioles, and many feel that variations in the tone of this abundant musculature may well influence blood flow through the lungs (Fig 199) While in the systemic circuit vasomotor constriction operates to distribute the cardiac output to organs having a variety of functions, it is generally accepted that each part of the lung has the same general function as any other part Therefore, the shunting of blood through various parts of the lung by arteriolar constriction would appear, if indeed it did exist, to have no particular functional

importance Furthermore, many of the "arteriolar" effects previously attributed to vasoconstrictor drugs on the basis of experimental data might also be attributed equally well to the effects of bronchospasm. The weak and contradictory responses of the pulmonary vessels to nerve stimulation and to the administration of drugs provides a rather insecure foundation upon which to ascribe pulmonary blood flow changes to alterations in vascular tone.

In direct contrast to the school which was designated by Rodbard as the "arteriolar tone school," there exists the "passivity school" which acknowledges the weak and equivocal responses of the pulmonary circulation to nerve stimulation and to the exhibition of potent response to cardiovascular drugs, this school holds that the lungs are essentially spongelike structures, passively accepting the right ventricular output "The blood flows passively downhill through the pulmonary vascular bed to the lower pressure of the left auricle." Even here, however, there are data which are difficult to harmonize with this theory The pulmonary arterial pressure (normally from 10 to 25 mm Hg with a mean of about 15 mm. Hg) may range from 30 to 80 mm. Hg mean pressure in patients with mitral valvular disease, congenital heart disease or in chronic cor pulmonale One would expect that were this entire load to be thrown on the pulmonary capillary bed pulmonary edema would quickly ensue Of course it can and often does ultimately ensue in these conditions but for many months and even years it may not do so Therefore there must exist some mechanism to prevent the full head of pulmonary arterial pressure from being thrust upon the capillaries in the alveolar walls. If increased arteriolar tone is not to be implicated in this circumstance then Rodbard suggests the possibility that this head pressure is "stepped-down" by increased bronchiolar tone This is not to deny that in the presence of chronic pulmonary hypertension definite changes do occur in the walls of the vessels comprising the pulmonary arteriolar bed, but such organic structural changes in the walls of vessels do not appear until pulmonary arterial hypertension has persisted for some time. Meanwhile, some mechanism would seem to be necessary to prevent pulmonary edema, the fluid in the alveolus represents the balance between alveolar capillary hydrostatic pressure and alveolar capillary colloid osmotic pressure—and the latter cannot be expected to increase significantly

By way of explaining how changes in bronchiolar tone might prevent development of pulmonary edema in the presence of pulmonary arterial hypertension, let it be recalled that positive pressure breathing is often efficacious in the treatment of pulmonary edema presumably by exerting an opposite pressure, forcing the fluid in the alveoli back into the pulmonary venous return to the left heart. It is suggested that during spontaneous recovery from pulmonary edema a contraction of the bronchioles produces air entrapment in the alveoli, resulting in an intrinsic positive pressure which similarly forces transudate back into the alveolar capillaries Parenthetically, it may be mentioned here that bronchospasm has long been considered to play a major rôle in the physiology and symptomatology (including pulmonary hypertension and subsequent cor pulmonale) of bronchial asthma, this is one instance in which bronchospasm probably does influence the flow of blood through the lungs

Regardless of its ultimate validity, the bronchiolar tone concept helps to make rational certain data derived during the treatment of chronic cor pulmonale As emphasized by Rodbard if the airways could be opened and the entrapped air be permitted to escape, much of the disability of chronic cor pulmonale would be dissipated. Actually, potent bronchodilators such as aminophylline and ephedrine have been shown to reduce the pulmonary arterial pressure despite an increase in cardiac output and a marked reduction in pulmonary vascular resistance is evident

Since it is generally accepted that bronchospasm contributes significantly to the symptomatology exhibited by the asthmatic, Rodbard suggested that bronchiolar constriction may be one cause of the increased pressure in the pulmonary artery and its minor subdivisions, apparently to protect the pulmonary capillary bed from an increased pressure. That asthmatic attacks have a large emotional element is also accepted, and Daly, Lambertsen, and Schweitzer[5] have presented evidence for the direct central control of bronchomotor tone, mediated through the vagus nerves. Therefore, while in pulmonary hypertension an organic element may exist in the form of medial and later intimal vascular thickening which may progress almost to occlusion of the smaller pulmonary vessels, a spastic element may be superimposed in the form of spasm of the bronchioles which in turn influences blood flow.

Tussive syncope. Fainting may follow a paroxysm of coughing in older emphysematous patients, and it has been suggested that this is the result of increased intra-alveolar pressure with back-stasis of blood in the systemic circulation leading to diminished cardiac output, similar to that produced by the Valsalva maneuver. The reduced cardiac output results in hypotension, which in turn results in cerebral anoxia and fainting. Cessation of coughing allows the intrapulmonary hypertension to diminish, with the result that cardiac output rises and consciousness is restored.

Acute pulmonary edema. This complication is particularly likely to occur under circumstances which predispose to left heart failure or to left atrial hypertension. Systemic arterial hypertension and myocardial infarction are especially common causes of the former, and mitral stenosis and mitral insufficiency are likely to cause the latter. Hormonal imbalance with sodium and water retention predisposes to pulmonary congestion. During operation, overtransfusion or excessive metabolic demands such as can occur in less than optimally controlled thyrotoxicosis may precipitate pulmonary edema. A pheochromocytoma may do the same. Excessive blood transfusion is a particular hazard following pneumonectomy and should be scrupulously avoided.

The onset of pulmonary edema is signaled by the appearance of excessive watery secretions in the endotracheal tube, perhaps associated with a fall in blood pressure. Auscultation of the chest reveals widespread râles, most marked in dependent areas. If the process continues, the clear secretions in the endotracheal tube become pink and frothy and virtually boil out of the tube when it is disconnected for suction. Without effective treatment at this stage the condition may soon terminate fatally.

Management consists of positive pressure oxygen therapy, elevation of the trunk, venous tourniquets to the extremities, aminophylline given intravenously, digitalis if indicated, and repeated catheter suction of the trachea. Of these, the first is perhaps the most efficacious.

PULMONARY ARTERIOVENOUS SHUNTS (FIGS. 174 AND 192). These defects were mentioned earlier. Although the presence of arteriovenous shunts bypassing the capillary circulation had been suspected from the passage of certain parasites through the lungs, Prinzmetal and his associates[18] were the first to demonstrate the passage of glass beads through the lungs of dogs and rabbits, and Tobin and Zariquiey[21] demonstrated this in man. The latter workers used fresh normal human lungs from 20 adults and 3 newborn infants which were perfused until they were almost free from blood. Several hundred small glass spheres ranging from 10 to 750 μ in diameter were then added to the perfusion. Spheres up to 500 μ in diameter were recovered in the perfusate from 9 adult and 2 neonatal lungs. Spheres larger than 500 μ were lodged in the arteries. By radiographs of lungs injected with radiopaque media, it was shown that shunts up to 500 μ in diameter are located near the apex of the lobes, shunts up to 200 μ in di-

ameter were found at lower levels and were occasionally present in the pleura.

Signs and symptoms If the shunt is significant in size, the common findings are those of *cyanosis* (due to the passage of unoxygenated blood directly from a pulmonary artery into a pulmonary vein) *clubbing* of the fingers and toes and usually, *polycythemia* A *murmur* may be heard and there may be a familial history of *hemorrhagic telangiectasis* An increased *density* may be seen on the plain roentgenogram and if angiography is done the density may further increase indicating that blood is flowing through it. Of course, an arteriovenous fistula may exist which is not sufficiently large to shunt enough blood to cause clubbing of the fingers or polycythemia.

It has been pointed out that cyanosis in *functional* pulmonary arteriovenous shunts is due to the passage of blood through poorly ventilated lung tissue An important point in diagnosis is that the breathing of 100 per cent oxygen will not raise the peripheral arterial oxygen saturation to normal if an A V shunt of significant size is present.

The *treatment* of true pulmonary arteriovenous fistula consists of excision of the lesion, usually with a portion of the surrounding lung.

PULMONARY EMBOLISM (FIG 200) This condition remains one of the outstanding unsolved problems in surgical practice. First, it is not a catastrophe that befalls only surgical patients, it is common in medical patients as well A second point of importance is that ***sudden death occurs in only about one fifth of the patients with this disease*** Towbin[22] conducted an autopsy survey at the Columbus State Hospital in Columbus, Ohio Between September 1, 1949, and January 1, 1954 881 deaths occurred. Postmortem examinations were performed in 512 cases (58 per cent) Of the 512 cases studied at autopsy, thromboembolic lesions were present in the lung in 132 (25 7 per cent) Massive pulmonary embolism was the cause of death in 73 cases (14.2 per cent) Occlusion occurred in arteries of medium caliber in 18 cases (3 5 per cent) Well established infarcts of the lung were noted in 60 subjects, representing 45 per cent of the cases in which there was embolic disease of the



Fig 200 Left A pulmonary embolus. The mechanism of death following small emboli is obscure Massive emboli may occlude the pulmonary artery to produce fatal cor pulmonale *Right* An infarct of the lateral segment of the right middle lobe

lung In many instances rapid death did not permit the development of definite infarction The most frequent site of embolization was the right lower lobe, being involved in 61 per cent of the cases in which there were thromboembolic lesions, though usually there were concurrent emboli in other lobes

Towbin divided the clinical patterns of pulmonary embolism into three main catagories *sudden death, a subacute course, and a chronic pattern* Sudden death occurred in 24 (18 per cent) of the patients in this study who had thromboembolic lesions in the lung Although the author noted that these cases demonstrated clinically the textbook picture of sudden and unexpected death, the attending physicians at the time often diagnosed coronary occlusion At autopsy it was found that 18 of this group had large, coiled, loosely impacted emboli in one or more of the lobar arteries In 6 instances of sudden death, emboli in medium sized pulmonary arteries constituted the principal finding at autopsy, in accord with the finding of de Takats and Jesser[6] that patients may die from a small embolus obstructing an insignificant area of the lung (due to the initiation of widespread autonomic reflexes?) If widespread spasm of the pulmonary arteries occurs to the degree that may be observed in the arterial spasm of the lower extremity following occlusion of a relatively minor branch, then it is of course possible that spasm of the entire pulmonary arterial tree could account for sudden anoxic death This has never been proved

In Towbin's series the subacute clinical pattern was observed in 55 cases, or 42 per cent of the deaths associated with pulmonary embolism and in 11 per cent of deaths occurring in all cases in which autopsy was performed in this study While there may have been an extensive pulmonary infarction in these patients, death did not occur for from several days to even a few weeks This is in sharp distinction to the generally held opinion that massive pulmonary embolism usually causes sudden death Towbin's study indicates that, on the contrary, *massive pulmonary embolism may cause a terminal illness which is prolonged over several days, and that this sequence is more common than that of sudden death* All clinicians have seen such cases, patients who were obviously mortally stricken at the outset but who survived for several days The following case is illustrative

Case study A middle-aged man was convalescing from exploratory laparotomy and biopsy of widespread pancreatic carcinoma when, 10 days postoperatively, he suddenly became cyanotic and apprehensive, and developed tachycardia Though in shock, he was completely rational The veins of the neck gradually became distended and the face suffused The electrocardiogram was within normal limits It was considered likely that the diagnosis was that of massive pulmonary embolism, which was proved at autopsy when he died approximately 3 days after the episode

This patient revived the question of pulmonary arterial embolectomy, since there was ample time for thoracotomy However, in 2 subsequent cases, both proved at autopsy, emergency angiography failed to demonstrate the site of the embolus

Finally, a chronic terminal illness was present in 53 (40 per cent) of Towbin's patients with thromboembolic lesions in the lung It was apparent that repeated embolization had occurred over a considerable period of time, and that pulmonary embolism had not represented merely the terminal event In 22 cases in this group there was massive pulmonary artery occlusion, these being mainly cases of ununited fracture of the femur in severely debilitated patients with large decubitus ulcers Femoral vein thrombi were usually found In this connection, Laufer and Gray[11] reported 2 cases of organized thrombus occluding a main pulmonary artery, and such a case was autopsied in our hospital

Pulmonary embolism is, again, not merely a sudden postoperative phenomenon, it often occurs repeatedly and may eventually cause pulmonary hypertension Towbin

found that the incidence increased with age and that, for some reason not readily apparent, it was more common in women than in men (34 per cent as against 20 per cent) In addition, it was noteworthy that patients with preexisting pulmonary disease appeared to suffer more severely from embolism than did patients with the same degree of embolism who had had no antecedent pulmonary disease. This of course again raises the question of whether or not these patients die of acute right heart failure, since lung disease might reduce the vascular bed and predispose to pulmonary hypertension. In conflict with the hypothesis of acute pulmonary hypertension and cor pulmonale as the cause of death, however, was the report of Selzer and Bradley.[4] They were performing cardiac catheterization when massive pulmonary embolism with shock occurred. The pressure in the pulmonary artery did not rise, it fell, and they suggested that peripheral (reflex?) failure is the cause of shock in pulmonary embolism

The cause of the fatal shock following pulmonary embolism remains obscure.

Acute and Chronic Pulmonary Emphysema

The term "chronic" is used here to differentiate the disease under discussion from "acute" pulmonary emphysema which is due to the ball valve effect of incomplete occlusion of a bronchus as from adenoma. The latter type of obstruction allows air to enter as the bronchus dilates on inspiration, but the air is expired with difficulty This causes overdistention of that portion of the lung supplied by the bronchus until the bronchus is completely obstructed even during inspiration and atelectasis results (Fig. 180)

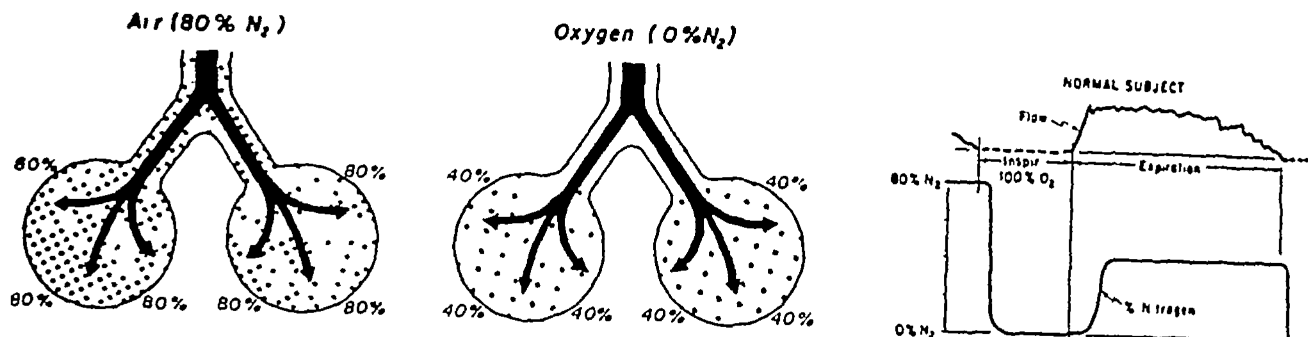
The etiology of chronic pulmonary emphysema has not been clearly determined but it is known to follow chronic cough, chronic bronchial infection, bronchospasm such as is commonly observed in bronchial asthma and other less well defined entities such as "senile degeneration. The residual lung volume is increased (Fig. 198), and poor gas mixing may be present (Fig. 201) *Carbon dioxide is not properly eliminated* and respiratory acidosis (Fig 194) may ensue, as will cyanosis due *to reduced arterial* oxygen saturation.

The emphysema may be expressed pathologically as diffuse hypertrophic emphysema, subpleural bullae and blebs, localized degeneration commonly referred to as "cotton-candy lung," or a combination of these Most workers feel that the elastic framework of the lung is weakened and that the *intrapleural pressure more nearly approaches* atmospheric pressure, due to the diminished *elastic recoil of the lung* Bronchostenosis and obstruction result in overdistention of the alveoli with resulting rupture of many of them which coalesce to form larger spaces, this may eventually result in a vast diminution in the total respiratory membrane surface available for the passage of oxygen into the capillary blood stream and for the escape of carbon dioxide A further result of this process is the obliteration of the capillary bed in the destroyed alveoli, with resulting diminished circulation through the lungs, this predisposes to the *development of pulmonary hypertension* and cor pulmonale (Fig. 149) Operation *upon an emphysematous lung is frequently* difficult because the lung will not collapse sufficiently to permit good exposure of the hilar structures. The development of respiratory acidosis under anesthesia must be carefully guarded against.

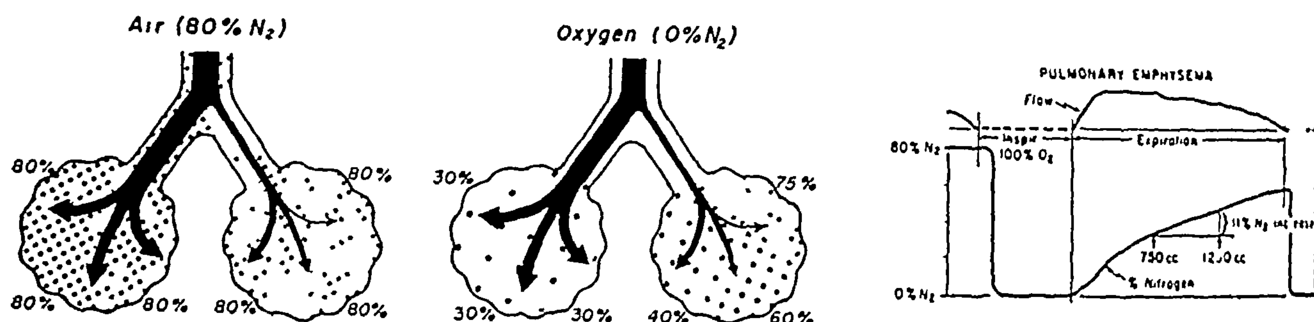
RELATIONSHIP OF ARTERIAL HYPOXEMIA TO DISABILITY IN EMPHYSEMA. The relationship of arterial hypoxemia to disability and to cor pulmonale with congestive failure in patients with chronic pulmonary emphysema was studied by Miller Fowler, and Helmholz[14] In 240 patients with chronic diffuse obstructive emphysema *the values for arterial* oxygen saturation were recorded by oximetry *with the patient at rest,* during exercise, and breathing 90 to 95 per cent oxygen. *Half of this group* maintained normal values for arterial oxygen saturation, even *after* exercise to the limit of their tolerance,

DISTRIBUTION OF INSPIRED GAS

UNIFORM DISTRIBUTION



NON-UNIFORM DISTRIBUTION



DISTRIBUTION OF INSPIRED GAS

Fig 201 Impaired gas mixing constitutes a major defect in the pathogenesis of chronic pulmonary emphysema (From COMROE, J H, JR, FORSTER, R E, II, DUBOIS, A B, BRISCOE, W A, AND CARLSEN, E *The Lung—Clinical Physiology and Pulmonary Function Tests* Chicago, Year Book Publishers, Inc, 1955)

while 23 per cent had hypoxemia at rest In an additional 27 per cent whose arterial oxygen saturation was normal at rest, hypoxemia developed during a standard exercise tolerance test It was found that although the incidence of hypoxemia was greater in patients with marked clinical disability, the presence or absence of hypoxemia did not govern the degree of disability in the individual case Many patients with hypoxemia had fairly good tolerance for exercise, whereas numerous patients with normal arterial oxygen saturation had severe exertional dyspnea On the other hand, cor pulmonale with congestive heart failure, when present, occurred almost exclusively among patients who had either transient or persistent hypoxemia, and the incidence was greatest among those patients with persistent hypoxemia Conversely, only 1 case of hypoxemia and cor pulmonale occurred among 118 patients in whom normal values for arterial oxygen saturation were recorded at rest

A basic problem in this disease is that of achieving adequate pulmonary ventilation without excessive physical effort (*i e*, respiratory "sufficiency" without respiratory "disability")

TREATMENT OF CHRONIC PULMONARY EMPHYSEMA In general, no truly satisfactory therapy exists, though considerable symptomatic relief may be provided *Medical measures* consist of bronchodilators, positive pressure breathing, abstinence from smoking, and treatment of pulmonary infection *Surgical measures* have included excision of large cysts and bullae, and vagal neurectomy The value of the latter is unproved

Intrathoracic Tumors (Fig. 202)

The principal physiologic disturbances that may be produced by intrathoracic tu-



Fig 203 Above X-ray showing huge right mediastinal mass which proved to be a lymphoma The total lung volume (and vital capacity) were considerably reduced. *Below* The surface of the tumor was traversed by many vessels, from which it gained its parasitic existence Such lesions often appear to be in part within the lung parenchyma, but usually a plane of cleavage can be established which permits ready separation of the lung from the surface of the tumor Lung volume and function were much improved following surgery

mors are (1) obstructive emphysema of the lung supplied by the partially occluded involved bronchus, followed by atelectasis and perhaps associated infection when bronchial occlusion by the growth is complete, (2) changes in lung function caused by diminished total lung capacity and vital capacity, (3) involvement of surrounding structures, such as the phrenic, sympathetic, or recurrent laryngeal nerve, (4) associated pleural effusion or esophageal involvement with dysphagia, perhaps leading to a broncho-esophageal fistula, (5) anemia due both to actual blood loss through hemoptysis or hemothorax and to an influence upon the red cell's life cycle, (6) distant effects such as clubbing, periostitis, and joint manifestations (p 181), and (7) toxemia due to necrosis and other less comprehensible factors which produce "malignant cachexia"

Lung Cysts

Various classifications of lung cysts have been offered, and there is still considerable disagreement as to precisely how the cysts arise For present purposes, however, the simple classification of congenital pulmonary cysts *versus* acquired pulmonary cysts will suffice

Congenital pulmonary cysts may be of the bronchogenic variety which are lined with bronchial epithelium but do not necessarily connect with a bronchus However, such cysts frequently do communicate with a bronchus and may be filled with fluid which is periodically disgorged When these cysts become infected they may be considered lung abscesses until removed They may be solitary or multiple Some disappear spontaneously

There is a second type of congenital cyst which is particularly likely to be found in the newborn, and this is the large balloon-like cyst or pneumatocele Respiratory distress may be a prominent feature in these infants, and excision of the cyst or the involved portion of the lung may be required to permit the remainder of the lung to expand

Finally, there may be combinatio both types

Acquired pulmonary cysts usually the form of bullous emphysema or pleural blebs Acquired "cysts" may follow pneumonitis in infants, these us clear with conservative therapy

As indicated, the *pathophysic* changes which accompany lung cysts ar to infection, to diminished lung volume pressure of the expanded cysts on surrc ing pulmonary tissue, and to rupture subpleural bleb causing spontaneous p mothorax It was formerly believed spontaneous pneumothorax was us caused by tuberculosis, but it is now cepted that the usual cause is the ruptu a subpleural bleb Pneumonitis may dev from spillage of cyst fluid

The infected lung cyst should be ex (Figs 203 and 204) Spontaneous pneu thorax is first treated conservatively aspiration of the air and, if repeated asp tion is necessary, by the institution of un water catheter drainage with suction to expand the lung If two or more attack spontaneous pneumothorax have occur it may be elected to perform thoracot and excise the cystic area which freque is obvious and often at the apex, to pre recurrence, one may strip the parietal pl over the area to produce pleural symph Some surgeons also introduce an irrita substance such as iodinated talcum pow to produce an inflammatory reaction wl will further promote pleural symphys

The management of cystic disease of lung where the cyst is not solitary—and pecially where cystic disease involves a jor portion of both lungs—presents a difficult problem In fact, this condition m be so extensive as to merit the common n of "vanishing lung" Under these circ stances it is not possible to excise most even a significant portion of the cystic l without unduly compromising the rema ing pulmonary reserve These patients m become pulmonary cripples and defy cessful therapy of any type



Fig 203 Left Congenital lung cyst with air-fluid level. The cyst had become infected *Right* Patient 1 week after operation The specimen is shown in Figure 204 She has remained well.



Fig 204 Left lung excised The entire organ was riddled with cysts of various sizes Four separate systemic arteries arose from the aorta near the diaphragm and entered this lung in addition to the distribution of the left pulmonary artery To sever these systemic arteries inadvertently in dividing the inferior pulmonary ligament can result in brisk hemorrhage

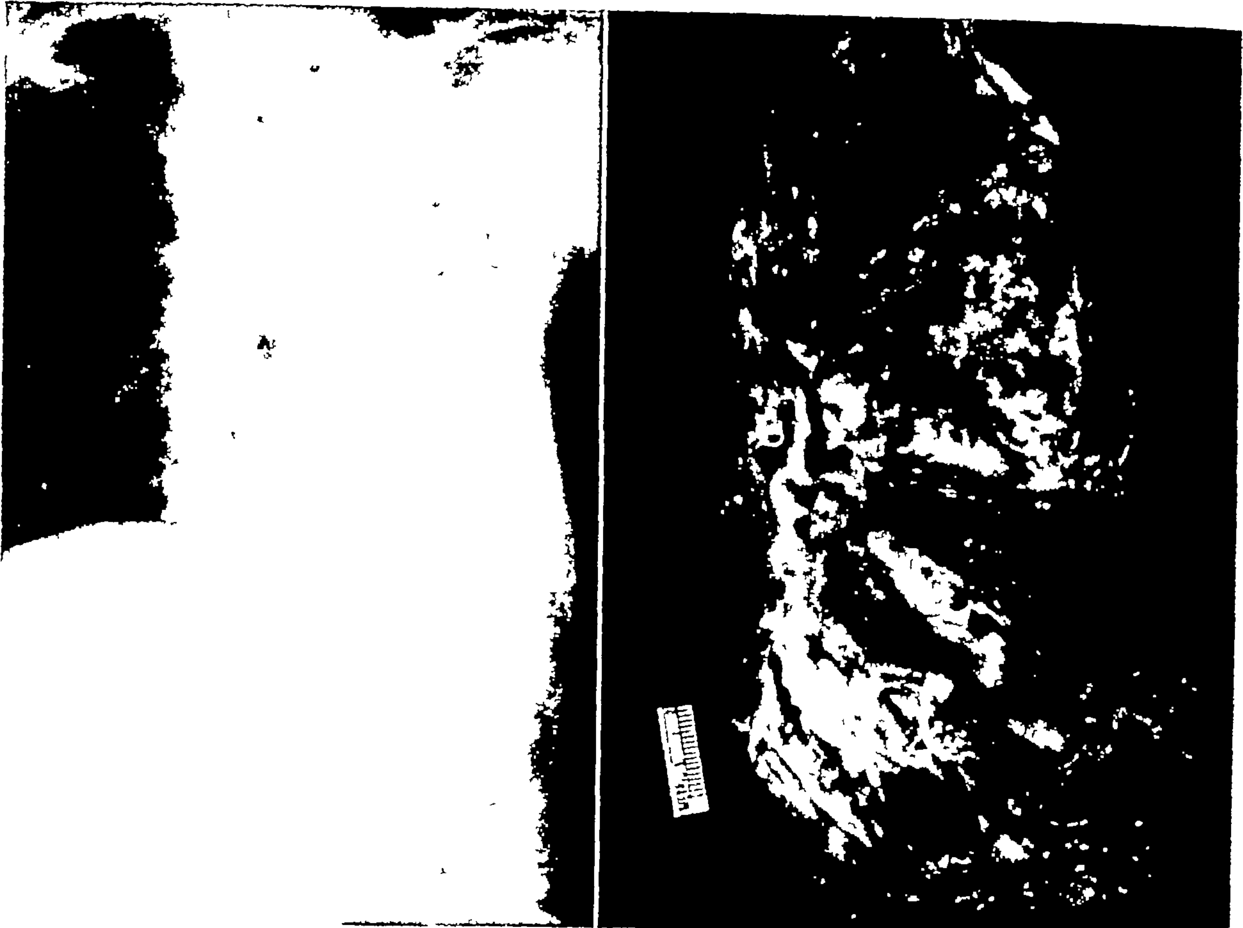


Fig 205 Left Bronchogram in adult female showing generalized bronchiectasis of left lung Copious sputum and constant infection The left lung was of little aid in respiration, in fact, it acted as a "functional shunt," since it was still perfused with blood, whereas the alveoli remaining were poorly ventilated Yet, she was not cyanotic at rest Vital capacity and maximum breathing capacity were diminished *Right* Excised left lung showing consolidation of upper lobe and extensive bronchiectasis of lower bronchi This lung was essentially useless in respiration, and pulmonary function was not impaired by removing this site of chronic suppuration

Chronic Pulmonary Infection: Bronchiectasis, Lung Abscess, and Tuberculosis

The derangements in normal physiology which result from chronic pulmonary infection are due, first, to the systemic effects of infection *per se* and, second, to the structural alterations produced locally that influence pulmonary function Bronchiectasis (Fig 205) and lung abscess (Fig 206), often referred to as "suppurative disease," are prone to develop following neoplastic bronchial obstruction, or perhaps following aspiration of foreign material, or distal to bronchostenosis due to cicatricial change Both diseases may be associated with considerable surrounding pneumonitis and, eventually, pulmonary fibrosis and atelectasis The usual signs of sepsis may be anticipated

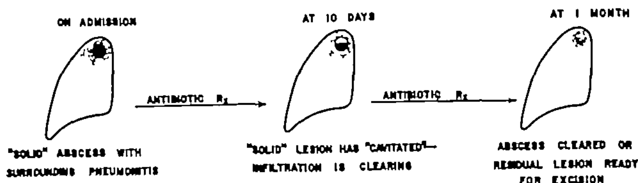
Tuberculosis, on the other hand, is above all a chronic, fibrosing process which may destroy a large portion of the pulmonary tissue Patients with bilateral, far advanced, widespread disease exhibit markedly reduced lung function and, not infrequently cor pulmonale and right heart failure

Clubbing of the fingers and toes may be a manifestation of almost any chronic lung infection or process, including that of fungus disease (Fig. 207)

In each of these diseases—suppurative bronchiectasis, lung abscess, and tuberculosis—it is important to comprehend the natural history of the process, for such knowledge is all but indispensable to intelligent diagnosis and management The terms acute, subacute, and chronic can represent highly important distinctions with respect

LUNG ABSCESS VS TUBERCULOSIS RATES OF HEALING

LUNG ABSCESS



TUBERCULOSIS

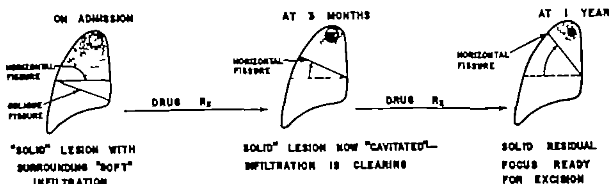


Fig 206 The hallmark of tuberculosis is its chronicity It heals by fibrous scar If an undiagnosed cavity diminishes rapidly under antibiotic therapy it probably represents a suppurative abscess rather than tuberculosis. Lung abscess is more common in the lower lobe and tuberculosis in the upper lobe.

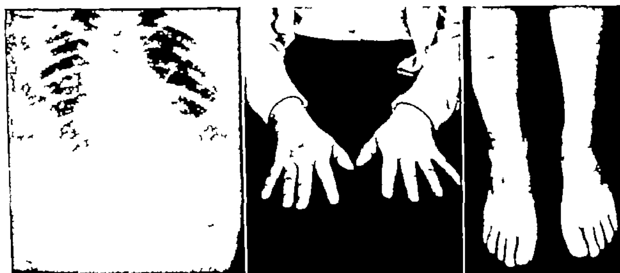


Fig 207 This patient had extensive bilateral pulmonary infiltration as seen on x-ray and, after repeated investigation in several medical centers, she underwent lung biopsy for diagnosis. Bacteriologic studies were negative but histologic studies were suggestive of either histoplasmosis or of perivascular cellular infiltration due to an irritative process. She lived in an area where *Histoplasma capsulatum* was endemic, but she had also been frequently exposed to chemicals used for cotton defoliation and as insecticides. She was usually dyspneic only on moderate exercise but at times this seemed *more marked im*mediately preceding menstruation. Note the clubbing of fingers and toes. She had extensive inflammatory pulmonary fibrosis of moderate degree. She was not cyanotic and polycythemia was not present. The vital capacity was reduced. The heart subsequently enlarged.

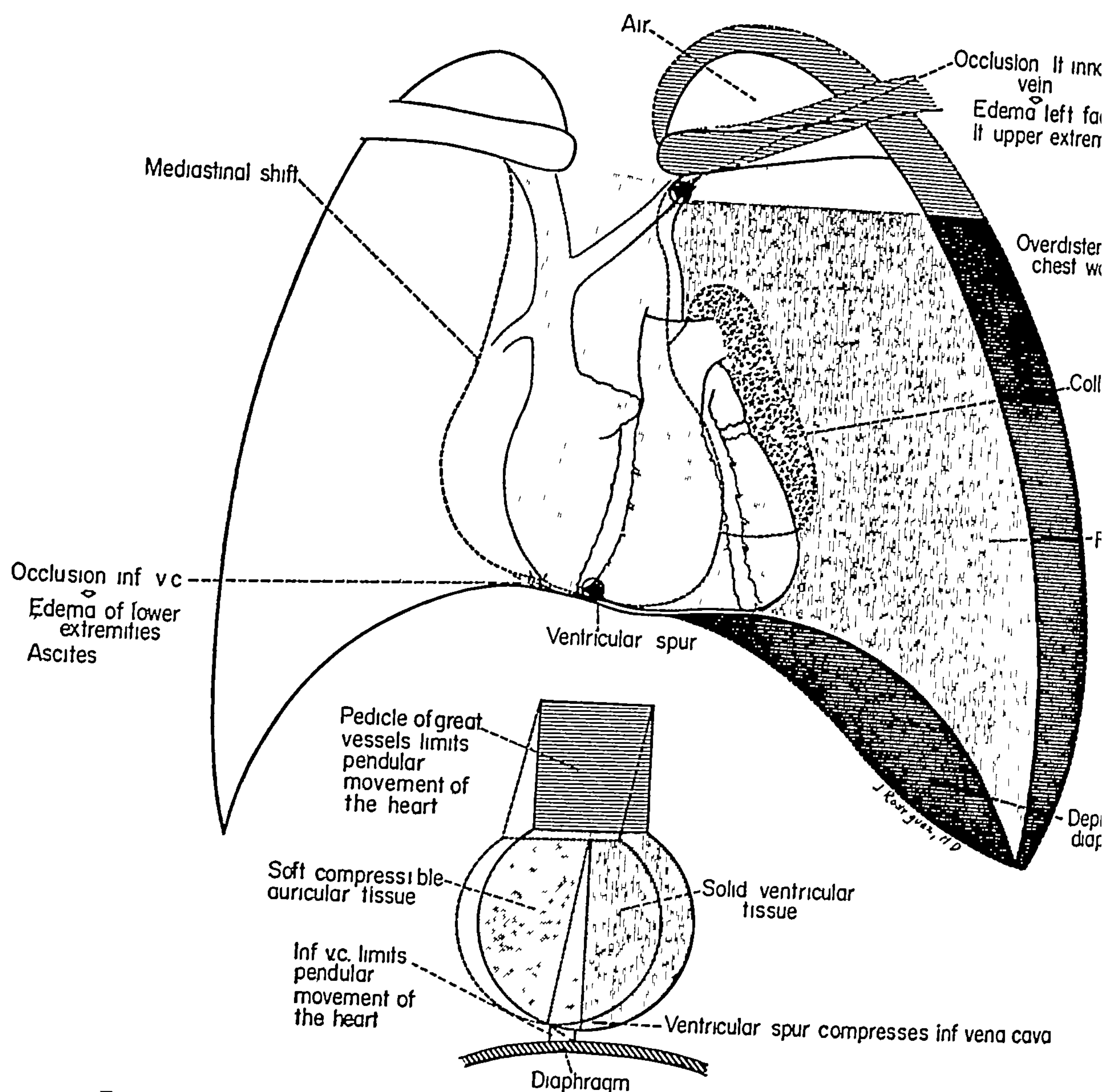


Fig 208 In this diagram are presented the clinical findings in an adult male who was admitted with a severe left pyopneumothorax Also indicated are the probable mechanisms by which selective edema of the left upper one-half of the body and the lower extremities was produced, there was no edema of the right face and arm It appeared probable that the left innominate vein had been occluded at the point indicated, while the right innominate vein remained patent The inferior vena cava was compressed by the ventricular spur as it shifted to the right Most significant, within a few hours after left thoracentesis the edema of the left face and arm and that of the lower extremities had largely subsided The severe cardiopulmonary symptoms had also diminished This case documents the effects of positive intrathoracic pressure, not only is the lung collapsed, but there is also an interference with the venous return to the right atrium

to prognosis and required therapy In Figure 206 it may be seen that a tuberculous cavity and a lung abscess cavity present many kinetic and therapeutic similarities In the former, one treats the acute "abscess" and surrounding exudative disease with strepto- mycin or isoniazid and *para*-aminosalicy acid (PAS), in the latter, penicillin in m sive doses is used If treatment is succe ful, the pneumonic or infiltrative element both diseases clears and the cavity dimi ishes in size—though this process may

expected to proceed far more rapidly in lung abscess than in tuberculosis, a point of diagnostic aid in doubtful cases. As time passes, the natural healing process of fibrosis and scar formation may entirely replace the cavity in either disease, or only a residual focus may remain. At this point the lung abscess is said to be "chronic" and the tuberculosis is said to have "stabilized," indicating that the time may have come to excise the remaining disease, which can now be done safely. As with peptic ulcer, surgery in tuberculosis and lung abscess is usually reserved for excision of disease remaining after medical therapy. And time is required to establish "intractability to further medical therapy." If the acute lung abscess is aggressively treated before fibrous tissue has surrounded it, more than two-thirds of such cases will not require surgery.

Thoracic Trauma

HEMOTHORAX, HYDROTHORAX, PNEUMOTHORAX, *FLAIL CHEST DUE TO MULTIPLE RIB FRACTURES*, AND SUCKING WOUNDS. Several aspects of thoracic trauma were described in Chapter 1, and are presented in Figures 1, 181, 183, 208, and 209. In general, most of these conditions interfere with normal lung expansion, either through occupying intrathoracic space or by rendering *it impossible to* achieve the negative intrathoracic pressure during inspiration that is required to expand the lungs. Pleural effusion, blood, and air compress the lung on the involved side and also displace the mediastinum to the opposite side partially to compress the second lung—*if the mediastinum has not been* fixed by previous inflammation. When any doubt exists and there is not time to get a chest x ray because of severe respiratory

STABILIZATION OF THE CHEST WALL

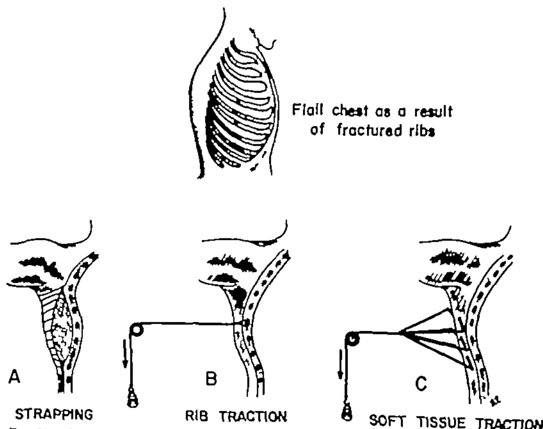


Fig. 209. Temporary strapping of the fractured ribs to secure immobilization and improve respiration is often highly expedient. Nevertheless, some type of traction or other means of rib fixation in normal position should be substituted for the compression as soon as practicable. Otherwise the ribs will heal in the depressed position and a serious reduction in lung volume may result.

distress, the chest should be aspirated immediately with a syringe and needle, indeed, even the needle may be lifesaving in the presence of tension pneumothorax

In flail chest and large sucking wounds an even more serious condition may obtain, for it is often even more difficult for the opposite "good" lung to expand In addition, the respiratory dead space is increased, "used" air is sucked to and fro between the "good" lung and the collapsed lung Effective ventilation may thus be brought almost to a standstill, and urgent measures are required The emergency management consists of strapping the defect Whether the injury consists of multiple fractures or an actual hole in the chest wall, the physiologic problem is the same Later some more fastidious treatment can be effected in the operating room on a live patient

In addition to the deranged pulmonary function in the presence of abnormal intrapleural pressures, the venous return to the right heart may be seriously interfered with (Fig 208)

Severe Hemoptysis: Causes and Management

Few complications cause more merited concern than does massive hemoptysis, for even if the patient does not exsanguinate he may drown in his own blood Fortunately, hemoptysis does not often represent a large volume and tends to be self-limited

Pulmonary bleeding is usually intermittent and usually stops with sedation and reassurance The Trendelenburg position should be used if bleeding is brisk, to avoid flow into the more dependent bronchi On the other hand, the bleeding may be such as immediately to threaten life Under these circumstances it is highly desirable to know the side from which the bleeding is coming Frequently the patient himself can lateralize the hemorrhage, on the basis of symptomatology If not, bronchoscopy may at least permit the identification of the involved main stem bronchus If this can be done and the bleeding does not lessen under conservative therapy, then once the offending side is identified one can rapidly perform thoracotomy and occlude that main bronchus Of course, the endotracheal tube must enter the "good" bronchus, and a steep head-down position must be maintained until the endotracheal cuff is inflated Frequent suction is indicated The clamping of the main bronchus ends the danger of bleeding into the uninvolved lung and one can then identify the involved lobe or smaller bronchus Bronchotomy may be required but the involved lobe or segment can often be identified by the external evidence of interstitial hemorrhage

Again, it is rare that emergency thoracotomy is required, and it is vastly preferable to identify the source with precision preoperatively Among the more frequent causes of profuse bleeding are bronchiectasis, tuberculosis, bronchial adenoma, and mitral stenosis In one patient who began to bleed at a startling rate during bronchoscopy, subsequent pulmonary arterial catheterization revealed marked pulmonary hypertension Large numbers of small varices were later visualized in the bronchial mucosa

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Chapter 17

The Physiology of Anesthesia: Some Points for Surgeons

The objective here is to survey some of the more practical physiologic considerations involved in the safe conduct of anesthesia Most anesthesiologists have a reasonably adequate understanding of cardiopulmonary physiology, but a very large number of anesthetics given in the United States are administered by persons who have received a very limited indoctrination in applied basic science Accordingly, the surgeon must develop, himself, a thorough appreciation of the physiologic problems that may arise in the patient who receives spinal anesthesia or who is put to sleep Even local anesthesia may produce alarming and at times fatal reactions

In preparing the factual discussion which follows, I have drawn upon several standard works in the field [1, 3, 7] However, most of the controversial opinions expressed are mine, and are not to be attributed to others

Rôle of Preanesthetic Medication

In contemplating surgery, the patient hopes for a reasonably pleasant and rapid passage to the unconscious state, from which he will awake cured of his disease The objective of preanesthetic medication is to increase the tranquillity and to enhance the safety of the anesthesia Basically, the tranquillity is ensured in most subjects by the use of a sedative, and the safety is enhanced both by sedation and by the use of an atropine-like drug to reduce tracheobronchial and oral secretions It also protects against certain circulatory reflex changes

The preanesthetic medication should begin the evening before operation with the administration of a suitable hypnotic, usually one of the barbiturates, to give the patient a good night's rest If the "usual dose" (such as 0 1 gm of pentobarbital) has not produced sleep by 1 or 2 o'clock in the morning, it is our practice to have this dose repeated On the morning of operation an additional sedative is given Formerly morphine was used almost routinely, but in recent years this respiratory depressant has generally been replaced by a barbiturate The latter has less effect upon respiration and, while it has little analgesic effect, the patient is not usually in pain prior to the operation anyway

If the dosage of the hypnotic has been adequate, the patient arrives in the operating room without apprehension and at times even asleep Having him in such a condition reduces the likelihood of a marked physical outburst during the second stage of anesthesia, and it also reduces the hazard of vago-vagal reflexes arising in the pharynx which may produce cardiac arrest Needless to say, it has much psychologic benefit in preparing the patient to face the operation

Inhalation Anesthesia

Broad Principles

RESPIRATORY FUNCTION AS RELATED TO ANESTHESIA The general physiology of respiration has been considered previously, but it is appropriate to reexamine certain specific

relationships that exist between lung function and the facility with which proper anesthesia can be established

The efficiency of inhalation anesthesia depends primarily upon the physical laws of the diffusion of gases. The problem is to deliver the anesthetic agent to the brain in the concentration required by the operation to be performed to hold it there in controlled concentration as long as it is needed, and to get it out again—all with the least possible interference with the normal physiologic process of the body (Fig. 210) The effectiveness with which anesthesia is induced will depend upon the following (1) the concentration of the anesthetic agent in the inspired air (2) the ventilation volume, (3) diffusion across the alveolar membrane and (4) the efficiency of the circulation

During the period in which anesthesia is being induced, the concentration of the anesthetic agent in the alveolar air is high relative to the concentration in tissues and there is ready flow of the gas to the cells. After the concentration of the anesthetic agent in the cells of the more peripheral tissues has risen to that approaching the concentration in the inspired air during which period anesthesia has been induced, there is much less rapid transport between the alveolar air and the tissues When the concentration of the anesthetic agent in the alveolar air is lowered at the end of the operation the gradient is reversed the high point of the gradient is now that of the concentration of the anesthetic agent in the cells and the low point is in the alveolar air (Fig 211) Therefore the cells are rapidly cleared of a large portion of the anesthetic agent the residual portion is eliminated much more slowly as the concentration in the cells begins to approach the low or virtually absent concentration in the alveolar air

The *minute respiratory volume* may have an equal or greater influence upon the diffusion volume of the agent across the alveolar membrane than has the factor of drug concentration in the inspired air For example the patient who takes only short,

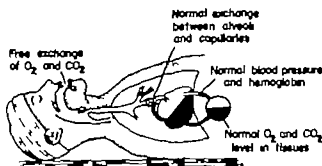


Fig 210 Some of the more important factors in the safe conduct of anesthesia (After American Medical Association *Fundamentals of Anesthesia* Ed. 3 Philadelphia W B Saunders Company 1954)

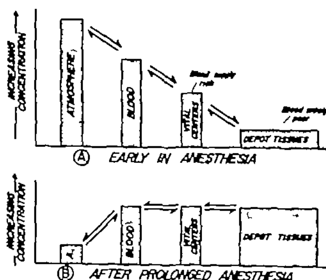


Fig 211 Direction of movement of anesthetic agent during induction and during recovery from anesthesia The depot tissue storage effect is a particular hazard in prolonged pentothal anesthesia, for example the injected pentothal cannot be exhaled as a gas and must be metabolized or excreted in the urine (After AMERICAN MEDICAL ASSOCIATION *Fundamentals of Anesthesia* Ed 3 Philadelphia W B Saunders Company 1954)

shallow breaths during an attempt at induction will be anesthetized slowly indeed regardless of the concentration of the anesthetic agent in the volume of gas that is inspired

Any circumstance which interferes with the transport of the anesthetic agent across the alveolar membrane will interfere with

ASPIRATION DURING ANESTHESIA

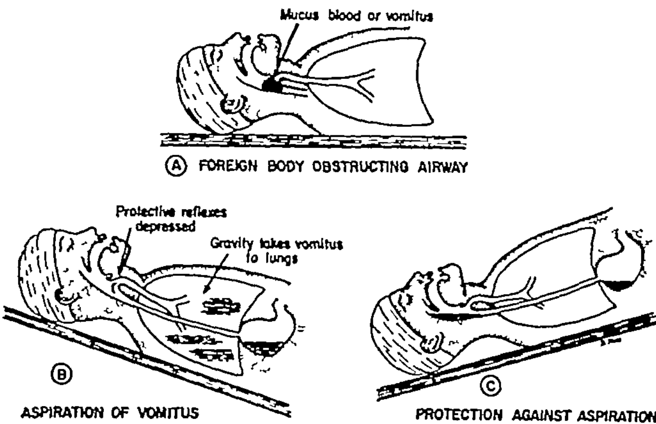


Fig 212 Some hazards during anesthesia

the process of anesthetization While mucus is the most common *barrier to diffusion* in inhalation anethesia (Fig 212), the presence of blood, purulent secretions, or of pulmonary edema may also interfere with gaseous diffusion

The efficiency of the *pulmonary and systemic circulations* influences the rate of transport to the cells of the brain, for otherwise the anesthetic agent will not be delivered to the brain in sufficient concentrations

Finally, some chemical agents act much more rapidly than others upon the cells of the brain Ether and chloroform do not affect the central nervous system nearly so rapidly as do nitrous oxide and ethylene Cyclopro-

Stage	Plane		
1st			1st STAGE – ANALGESIA
2nd			2nd STAGE – DELIRIUM
3rd	1	3rd STAGE SURGICAL	1st Plane
3rd	2		2nd Plane
3rd	3		3rd Plane
3rd	4		4th Plane
4th			4th STAGE – RESPIRATORY PARALYSIS

Fig 213 This chart shows the division of anesthesia into four stages and the division of the third or surgical stage into four planes (From GUEDEL, A E *Inhalation Anesthesia—A Fundamental Guide*, Ed 2 New York, The Macmillan Company, 1952)

pane acts rapidly, is capable of producing all stages of anesthesia, and permits rapid recovery

Stages and Planes of General Anesthesia

The stages and planes of anesthesia are represented graphically in Figures 213 and 214 These are relatively easily remembered when one has closely observed anesthesia induction a few times

Stage I, or the stage of *analgesia*, is that produced by one or two inhalations of a nitrous oxide-oxygen mixture such as is commonly used by dentists for dental extractions The senses are benumbed but the patient remains conscious The period of analgesia is brief, but it is adequate for very short procedures *Stage II*, or the stage of *delirium*, is often a stage of excitement, representing the time when the individual loses consciousness The higher centers of cerebration are blocked, leaving the secondary centers active The patient may pass very quietly through this second stage, or the most violent outburst may be noted It is advisable always to have the patient adequately restrained by suitable harness or by assistants who guide the individual's movements but protect the conduct of the anesthesia During this stage all should be quiet and the patient should not be molested He can often still hear, but he may grossly misinterpret what he hears The second stage may again be observed as the whole process of anesthetization is reversed and the patient is emerging from the anesthesia

Stage III, or the stage of *surgical anesthesia*, is the one in which surgical procedures become possible This third stage extends from the onset of regular rhythmic respiration and loss of the eyelid reflex to *Stage IV*, or the stage of *respiratory paralysis* *Stage III* has been subdivided into four planes

The Signs of the Various Stages and Planes of General Anesthesia

The presence or absence of Stage I and Stage II can usually be detected by super-

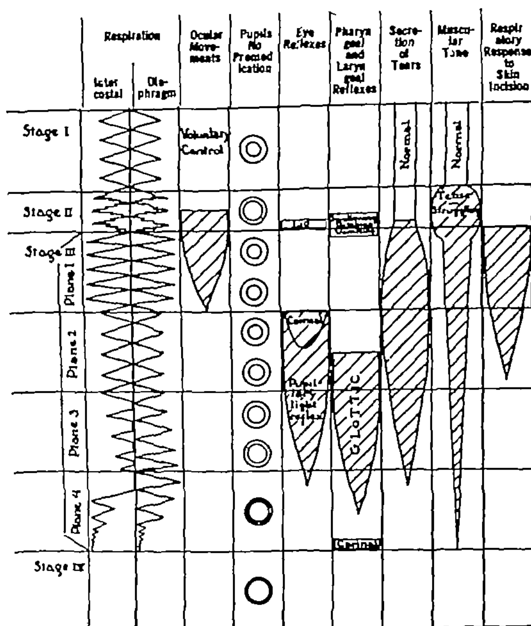


Fig 214. Physical signs of depth of anesthesia. It is important that the surgeon know the physical signs upon which the anesthesiologist depends to guide the course of the anesthesia. (From American Medical Association *Fundamentals of Anesthesia* Ed 3. Philadelphia, W B Saunders Company 1954)

ficial observation. However, Stage II, or the stage of delirium, may be misleading in that the patient may appear to be in the early planes of Stage III when in fact he may suddenly begin violent struggles and have to be forcibly restrained

As noted during Stage II it is preferable to avoid all possibly exciting influences such as mention of the operation within the patient's hearing or the beginning of the prep

The planes of Stage III are to a considerable extent arbitrary, but is useful to be able to distinguish in a general way between the lighter planes and the deeper planes.

CHARACTERISTICS OF THE PLANES OF STAGE III (SURGICAL) ANESTHESIA. In Plane 1 of Stage III the eyeballs usually are moving and strabismus may be present the lid reflex is inactive and superficial skin reflexes are dulled. The respirations are now regular with inspiration and expiration being of equal length. The swallowing reflex is abolished and the pupils are of preanesthetic size In *Plane 2* the eyeballs are now inactive and are fixed centrally with a slight increase in the size of the pupil The abdominal muscles are beginning to relax. In *Plane 3* the eyeballs are still fixed and the pupils slightly

more dilated The pupillary light reflex is present but becomes progressively more sluggish as the depth of *Plane 3* is increased Muscular relaxation is adequate for abdominal surgery In *Plane 4* the eyes are fixed and the pupils are widely dilated, as a rule The pupillary light reflex is abolished Profound skeletal muscular relaxation is present and bronchial reflexes are obtunded *With cardiorespiratory paralysis not far distant, the blood pressure and the pulse pressure tend to fall, and the pulse rate increases Respiration is of the gasping type and is much less effective These are important warning signs*

In *Stage IV*, or the stage of respiratory paralysis, there is a cessation of automatic respiratory function (Respiratory paralysis is deliberately induced in the course of the so-called "controlled respiration" anesthesia that is used in certain intrathoracic operations Here the anesthetist maintains the pulmonary ventilation by rhythmic manual compression of the gas bag, otherwise, of course, death from anoxia would supervene However, respiratory efforts may be largely abolished with a lesser degree of anesthesia if the lungs are continuously hyperventilated to reduce the CO_2 stimulus) In Stage IV there is complete absence of reflex activity and the pupils are widely dilated (except under cyclopropane) and are inactive to light

The stages and signs of anesthesia were developed largely with the use of ethyl-ether anesthesia When the patient is under cyclopropane there is more depression of respiration but less effect upon the pupils Whereas dilatation of the pupil often occurs in Plane 4 of surgical anesthesia when ethyl-ether is used, with the administration of cyclopropane a pupil that is more than 25 per cent dilated over the preanesthetic size is rarely seen unless hypoxia is present In this connection, it is worth remembering that nitrous oxide alone is incapable of inducing a depth of anesthesia much beyond Plane 2 of Stage III without producing definite and visible hypoxia Accordingly, to provide surgical anesthesia, nitrous oxide is usually supplemented with some other agent such as Pentothal or ether, often with the aid of a muscle relaxant such as the curare-like agents.

ADDITIONAL COMMENT While the eye signs are of contributory aid, *the safest means of evaluating anesthesia usually consist of the character of the respiration, the level of the blood pressure, and the state of muscular relaxation* A dilated pupil may be due to sympathetic stimulation, perhaps from fear or other factors, and it may be necessary to test for the light reflex to distinguish sympathetic dilatation from that caused by hypoxia or an overdose of the anesthetic agent If the light reflex is also absent in the presence of pupillary dilatation, the probability of hypoxia or anesthetic overdose must be considered

The reason that very deep surgical anesthesia is particularly hazardous in less experienced hands is that the number of clinical guides to the level of the anesthesia declines progressively as the depth of anesthesia increases

Reflexes of Importance in the Conduct of Anesthesia: Further Comment

THE EYELID REFLEX This reflex is elicited by gently raising the upper eyelid If the patient is still in the second stage of anesthesia the eyelid will then descend and will close However, if the anesthesia is in the third stage the lid will not close spontaneously This affords a means of determining whether the patient is in the stage of delirium, though quiet, or whether he has reached Stage III, that of surgical anesthesia

REFLEX SWALLOWING The appearance of swallowing indicates that the patient is "light" It is usually noted in the first or uppermost plane of Stage III, if the patient is coming out of deep anesthesia When one is operating upon animals, the observation that the animal is making swallowing movements is a signal to administer additional anesthesia.

VOMITING This frequently occurs as the

patient emerges from anesthesia or as he is being inducted. It is met at the deep end of second stage anesthesia and is only slightly above the level at which reflex swallowing is noted. The danger of vomiting is, of course, that in the absence of a snugly fitting endotracheal tube the patient may aspirate vomitus into the lungs (Fig 212) Death may occur abruptly or, if not, lung abscess or pneumonitis may develop

REFLEX APNEA. Apnea may be defined as the absence of respiratory efforts It is seen particularly at the beginning of anesthesia induction (reflex) and at excessive depths of anesthesia (paralysis) Or hyperventilation may have so lowered the blood CO_2 tension (acapnia) that the usual respiratory stimulus is lacking. Actually, hyperventilation prior to reflex breath holding may permit the maintenance of apnea for a considerable period of time. Eventually however the concentration of carbon dioxide will reach a level at which the patient will no longer be able to hold his breath voluntarily

LARYNGOSPASM. While reflex laryngospasm or spasm of the vocal cords is at times produced by traction on abdominal viscera the most common and annoying type of laryngospasm is that which follows direct irritation of the vocal cords usually by the anesthetic agent. Varying degrees of spasm are frequent with ether but less so with cyclopropane The presence of such spasm indicates that the level of anesthesia is above the second plane of Stage III, since it is abolished at the junction of the first and second planes of third stage anesthesia. Spasm is particularly likely to occur if a high concentration of irritating anesthetic mixture is employed initially With mild spasm it may be possible to maintain adequate oxygenation by compressing the bag while waiting for the spasm to be broken through

Severe laryngospasm is a most common serious complication in anesthesia and time is a critical factor The first corrective action should be moderately strong intermittent positive pressure on the rebreathing bag with 100 per cent oxygen. If no gas has been forced past the cords after about 30 seconds, critical time should not be wasted with ineffectual measures. The patient should be totally relaxed with one of the intravenous muscle relaxants, of which Succinyl Choline is the fastest While waiting out the 45 seconds required for Succinyl Choline to act, positive pressure should be continued on the bag The instant the cords begin to relax oxygen will be forced into the lungs The patient should be ventilated with intermittent positive pressure until he appears to be well oxygenated An endotracheal tube should now be inserted It must be realized that once a muscle relaxant is used the patient will not breathe spontaneously for at least several minutes. In every anesthetic the anesthetist must be prepared to control ventilation by mask and to intubate if this should become necessary

VAGO-VAGAL REFLEX. Laryngeal or tracheal stimulation or irritation during the introduction or the removal of an endotracheal tube particularly under certain conditions of respiratory disequilibrium, may produce marked effects upon the heart. The vagus nerves supply both the afferent and the efferent fibers of these reflexes Cardiac arrhythmias such as bradycardia, atrioventricular (A-V) block cardiac standstill or even ventricular fibrillation may occur It appears that this may be more likely when cyclopropane is being used than with other anesthetics, with the possible exception of intravenous Pentothal

TRACTION REFLEXES Reflexes produced by traction may be readily observed during either abdominal or thoracic surgery Those in the abdomen generally result from traction on the mesentery or on various viscera. Changes in respiratory or circulatory function or vomiting may ensue

In the thorax the reflexes which result in variations in respiration or in cardiac activity result from traction in the region of the hilum which stimulates the abundant vagal fibers. Many surgeons prefer to anesthetize the region of the hilum of the lung before beginning the hilar dissection.

SKIN REFLEXES One reason that it is important to have the blood pressure checked from time to time when relatively minor operations are being done under local anesthesia is that reflex hypotension may develop

Controlled Respiration

Previous reference has been made to the fact that the respiratory reflexes can be abolished and the ventilation provided entirely by manual or mechanical means This technic is facilitated by the use of cyclopropane, since this agent has a markedly depressant effect upon respiration, however, controlled respiration can also be achieved with other agents

Technic When the third stage of anesthesia has been reached, the rebreathing bag (Fig 215) is squeezed during the latter portion of each inspiratory phase, the bag being promptly released as normal expiration begins By careful timing of the manual pressure on the bag with the patient's respiratory efforts, pulmonary hyperventilation can be produced This reduces the content of the carbon dioxide in the alveoli air and the blood, and at the same time the increased respiratory volume results in an increased diffusion of the anesthetic agent When the blood content of carbon dioxide has become sufficiently low and the tissue content of ether sufficiently high, spontaneous respiratory movements cease The anesthetist then carries on the respiration as necessary at a rate slightly exceeding the normal respiratory rate, perhaps at 20 to 22 respirations per minute When desired, the spontaneous respiration can be restored by maneuvers which diminish the concentration of the anesthetic agent in the tissues or which increase the concentration of carbon dioxide available for the stimulation of respiration, or both Hyperventilation can also be effected with some artificial device such as the Jefferson ventilator

The dangers attendant upon deep anesthesia consist chiefly of overdosage of the anesthetic agent, and hypoxia and hypercapnia from inadequate respiratory ventilation Controlled respiration is a type of anesthesia which is to be used only by the more experienced person, specifically, it should not be used by the anesthetist who has not had sound training in respiratory physiology Controlled respiration is not required for most thoracic operations

Controlled hypotension during anesthesia is discussed elsewhere (p 363)

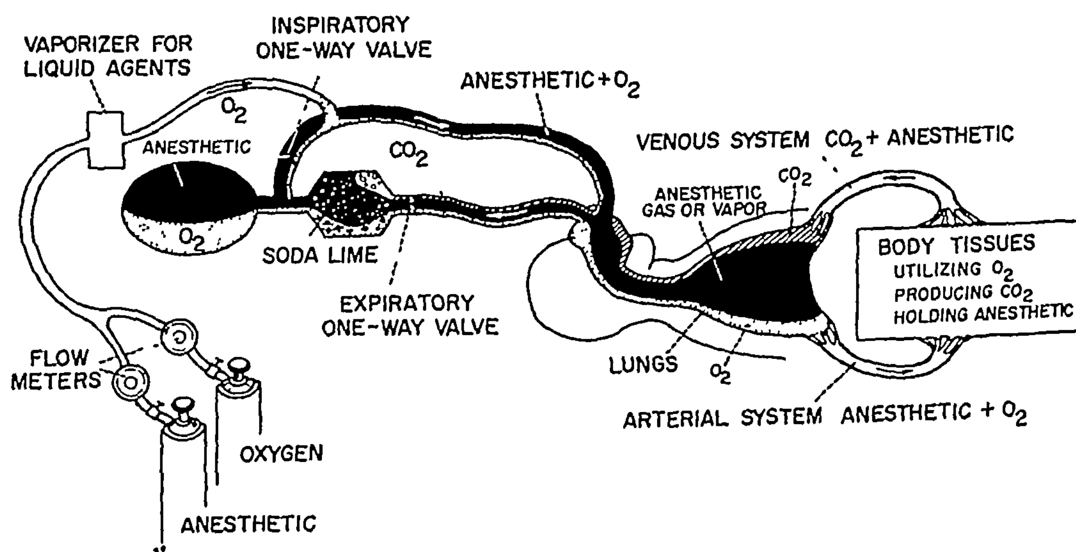


Fig 215 The common gas machine (After Adriani, J, in American Medical Association *Fundamentals of Anesthesia* Ed 3 Philadelphia, W B Saunders Company, 1954)

Commonly Used Anesthetic Agents

Some Volatile Liquids and Inhalation Gases

ETHYL ETHER. This drug was first used to induce anesthesia in human beings by Crawford Long in 1842, but its use was not officially reported until employed by Morton in 1846. Ether volatilizes rapidly during open administration at room temperature, and thus effects a cooling of the atmosphere inspired by the patient. The effective concentrations of ether vapor for anesthesia are from 3.5 to 4.5 per cent, and overdosage may occur when alveolar concentration is from 6.7 to 8 per cent. Ether is not altered in the body and approximately 90 per cent of the inhaled ether is eliminated through the lungs, the remainder being eliminated through the skin and urine. The average time of desaturation is 8 hours, though in obese individuals this may require a longer period of time. And it certainly will require more time if the individual has received excessive amounts of ether for anesthesia. The emergence from ether anesthesia can be hastened by hyperpnea and slowed by diminished respirations.

Drucker and his group[6] have emphasized that ether results in such abnormalities of glucose metabolism as to simulate uncontrolled diabetes.

CYCLOPROPANE. The anesthetic properties of this drug were first recognized by Lucas and Henderson[8] in 1929, and an early clinical report was made by Waters and his associates[9] in 1934. This agent is a saturated hydrocarbon gas, colorless and with a sweetish garlic-like taste and odor. It is nonirritating to the mucous membranes in concentrations of under 50 per cent. Cyclopropane is essentially as potent an anesthetic agent as ether. It has with chloroform the property of increasing the irritability of the cardiac conduction mechanism. In general, however, cyclopropane is well tolerated. Its marked respiratory depressant effect renders it an effective agent for establishing controlled anesthesia; this is safely achieved because, since only comparatively small concentrations of the gas (20 to 25 per cent) are required to produce anesthesia, the oxygen concentration in the inspired gas mixture can be on the order of 80 per cent. In contrast, since ether is in many respects a respiratory stimulant, the administration of adequate amounts of the ether to produce respiratory arrest would require a dangerously high concentration if no element of hyperventilation were used. Analgesia may be produced with from 3 to 5 per cent cyclopropane in the gas mixture, unconsciousness with 6 to 8 per cent, surgical anesthesia with 20 to 25 per cent, and respiratory arrest with from 35 to 40 per cent concentration.

Cyclopropane-oxygen represents a more explosive gas than does ether oxygen, and it is also associated with a greater incidence of arrhythmias. Cyclopropane produces less muscular relaxation than does ethyl-ether, but the use of curare-like compounds has largely obviated this defect.

Again, a particular advantage of cyclopropane is that a low percentage of drug in the gas mixture permits a high concentration of oxygen. However, associated respiratory depression may permit adequate oxygenation (by virtue of the high oxygen concentration) even while acidosis develops from inadequate ventilation that results in carbon dioxide retention.

NITROUS OXIDE. While nitrous oxide is in itself a virtually nontoxic agent, it alone cannot produce satisfactory surgical anesthesia with adequate relaxation. Unfortunately, the occasional anesthetist achieves surgical anesthesia by virtue of the element of relaxation that is derived from anoxia. This agent should not be employed in concentrations greater than 80 per cent nitrous oxide (the other 20 per cent of the mixture being oxygen), certainly not for surgical anesthesia.

Nitrous oxide, to repeat, does not produce satisfactory relaxation. It is the familiar "gas" anesthesia that is so commonly used by dentists. For prolonged surgical operations the nitrous oxide–oxygen mixture is

usually supplemented with ether or Pentothal The failure to produce relaxation can be partially offset by using curare

The use of nitrous oxide is contraindicated in the presence of anemia

Intravenous Agents

THIOPENTAL SODIUM (PENTOTHAL SODIUM) When given intravenously this barbiturate produces a rapid and profound hypnosis and, soon, unconsciousness In essence, the patient is either awake or asleep One convenient form of administering the drug is to ask the patient to begin counting, the drug is then injected slowly until the individual can no longer continue

One form of the drug may be dissolved in 40 cc of distilled water and then given intravenously The rate of injection should not exceed 4 cc in the first 15 seconds, at least 30 seconds to 1 minute being permitted for the full effect of the preliminary injection to occur The initial dose can then be repeated if the narcosis does not develop within 40 seconds After the patient is unconscious, from 1 to 2 cc are injected intermittently, as required, to maintain the unconscious state

The *advantages* of Sodium Pentothal anesthesia are that the induction is rapid and usually pleasant for the patient, moreover, recovery is prompt (if an excessive dose of the drug has not been given) and is not unpleasant Pentothal produces little or no nausea, it is free of the usual explosive hazards, and the cough reflex is not abolished Salivation and pulmonary secretions are not increased It is particularly valuable for the induction of cyclopropane or ether anesthesia in persons who are apprehensive Passage of an endotracheal tube is often facilitated by the use of Pentothal, even when the anesthesia is to be continued with another agent Pentothal is often used in combination with nitrous oxide by inhalation, and with curare by injection, for complete surgical anesthesia When Pentothal is used alone, suitable muscular relaxation is not obtained without the addition of curare

Definite *disadvantages* are encountered with Pentothal anesthesia To begin with, it is a strong respiratory depressant and once injected it cannot be rapidly eliminated ether can be exhaled, but Pentothal must be metabolized by the liver or excreted Furthermore, the drug is stored in depot tissues such as fat and progressively more may need to be injected to keep the concentration in the brain at an anesthetic level Yet, the accumulation in the depot tissues may inordinately prolong recovery from anesthesia if Pentothal is used for a long operation Thus, it is desirable to limit its use to suitable procedures which require only about 30 minutes of anesthesia

Second, as it is a barbiturate, it has little analgesic effect Third, there are fewer reliable signs of anesthesia than with ether It is therefore difficult to maintain the level of anesthesia at a point that is between the stage of decreased reflexes and that of respiratory or circulatory depression In inexperienced hands this respiratory depression is the major hazard of the drug Admittedly, in the hands of an expert Pentothal represents an extremely useful drug, especially for the induction of other anesthetics and for the insertion of the endotracheal tube where this is to be used In contrast, in the hands of those who are less familiar with this agent its use can be disastrous The following case report is illustrative

Case study The patient was a 54-year-old white woman with mitral stenosis who had been essentially bedridden for the past several months She of course represented a poor surgical risk, but the internist in attendance and the patient herself and her family thought that the possibility of benefit from a mitral valvulotomy was worthwhile, in view of her present life as an invalid Accordingly, after she had been hospitalized and prepared as best she could be, she was brought to surgery There the anesthetist, who rarely used Pentothal for any purpose, decided that on this particular occasion the drug would reduce apprehension and facilitate intubation A "usual dose"

was given intravenously, following which the respirations promptly ceased and did not resume for almost 30 minutes Intubation was not readily achieved, and meanwhile it proved difficult to inflate the lungs adequately by compression of the gas bag. Her appearance was one of deep cyanosis. Eventually some degree of spontaneous respiratory activity did return, however, and the skin color improved to approximately that present preoperatively

At this point consultation was held with her internist and the anesthetist It was agreed that, ordinarily, good judgment would dictate postponement of surgery but that in her case, it was doubtful whether further delay would be tolerated. Moreover, since the endotracheal tube was now in place and fairly adequate pulmonary ventilation possible, it was elected rapidly to execute the mitral valvulotomy This was done satisfactorily and uneventfully through the bed of the excised left 5th rib Finger fracture sufficed No anesthetic other than the initial Pentothal injection was given

Only once was further physiologic difficulty encountered during operation As the atrial appendage was being oversewn the heart rate became slow and cardiac contractions weak but at no time did the heart stop At the end of the operation the blood pressure had fallen from an initial level of 100/60 to a level of 70/40, though this gradually rose Respiration remained unsatisfactory and it was some time before extubation and discontinuance of manual assistance could be achieved Eventually she was returned to her room in fair condition with orders that respiration was to be closely watched It remained shallow and slow and 4 hours postoperatively the rate fell rather abruptly to 4 per minute and the blood pressure fell to shock levels She still had not reacted in any manner and all reflexes were absent Recall too that no anesthetic had been given during the entire operation except for the initial injection of *Pentothal* It was believed that the patient simply had never metabolized the original dose of Pentothal, though its respiratory depressant effect might have been augmented by the period of anoxia which had occurred prior to intubation. A face mask and anesthesia machine were employed to improve pulmonary ventilation, using the airway that remained in place from operation Her color promptly improved considerably and spontaneous respiratory efforts quickened, possibly due in part to the injection of caffeine and Coramine Nevertheless, the rate was still only about 12 per minute and the excursions were very shallow Accordingly it was decided to give the patient Nalline (N allylnormorphine), though it was appreciated that this drug was generally considered to be only a morphine antagonist and not a barbiturate antagonist Nevertheless, shortly after 10 mg. had been injected intravenously both the rate (to 20 per minute) and depth of respiration improved considerably After a period of time an additional 10 mg of Nalline were given intravenously Thereafter the patient began to move her hands and feet slightly and within the next 30 minutes she began to moan intermittently All this was viewed as an encouraging turn of events but unfortunately 10 hours later she suddenly became markedly hypotensive again and nor epinephrine and transfusion were ineffectual in raising the blood pressure. She died

Comment A number of factors contributed to this patient's death. A major contributory cause was of course, the Grade IV heart disease due to mitral stenosis. Second the use of Pentothal represented poor judgment especially in this critically ill subject —and particularly as the anesthetist was not adequately familiar with its capacity to depress respiration. Again Pentothal should be used only by the expert. This particular anesthetist was especially facile in the use of ether for pulmonary resections, but she simply chose to use an unfamiliar drug in an extremely poor risk patient. Actually the dosage given would not have been excessive in most subjects, but in the patient in question who had chronic passive congestion of

the liver and whose edema-free weight was only 90 lb , it was excessive Lastly, in retrospect, when there was difficulty with the induction we should have postponed the operation, even if there was the strong possibility that conditions might not again be even as stable as they appeared then

To repeat, once Pentothal has been injected it cannot be removed until metabolized or excreted in the urine Ether is much safer in the hands of the less experienced person

Spinal Anesthesia

Agents for Spinal Anesthesia

The three drugs most frequently used for inducing spinal anesthesia are *Nupercaine, Pontocaine, and procaine*

TECHNICS Spinal anesthetic solutions are either *hyperbaric* (having a specific gravity greater than that of spinal fluid) or *hypobaric* For example, procaine dissolved in spinal fluid is mildly hyperbaric If dissolved in a heavy glucose solution (10 per cent), however, it becomes definitely hyperbaric and tends to gravitate to the lowest part of the spinal sac Nupercaine, on the other hand, in a 1 1500 solution is definitely hypobaric and tends to rise in the spinal sac Thus, by using solutions of anesthetic drugs that are heavier or lighter than spinal fluid, the anesthetist can by posturing the patient direct the flow of the anesthetic agent upward or downward Nevertheless, this must be done promptly, before the agent has been "fixed" by the nerve tissues After such fixation, changing the position of the patient may no longer affect the level of anesthesia

Hypobaric solutions must be used with care in that they tend to rise unless the patient is put in a Trendelenburg position With hyperbaric solutions, on the other hand, the patient is first put in a Trendelenburg position until the level of anesthesia, as tested with a pin, has risen to a point that is suitably high to permit the intraabdominal procedure that is contemplated He is then returned to the horizontal position to prevent a further rise of the anesthetic agent The chief danger of allowing the drug to extend too far upward is, of course, first, the paralysis of the muscles of respiration including the diaphragm and, later, even paralysis of medullary centers

LENGTH OF ACTION Procaine has a relatively short action A dose of this drug will produce dependable anesthesia for only 1 hour, as compared to comparable doses of Pontocaine and Nupercaine, both of which produce anesthesia of from 1 to 3 hours Since it is always possible that the duration of operation will be longer than anticipated, Pontocaine and Nupercaine are usually preferred to procaine

The use of Pontocaine is particularly satisfactory This drug is far more potent than procaine and is used in one-tenth the concentration of the latter, that is, in a solution of from 0 5 to 1 0 per cent (20 mg) This dilution usually affords approximately 2 hours of anesthesia, which is adequate for most of the more common operations such as cholecystectomy, colectomy, or herniorrhaphy It is of course not adequate for operations which upon occasion take longer, such as gastrectomy, abdominoperineal resection, and the like Nevertheless, the technic of "continuous spinal" may be used for an operation of almost any duration, the catheter or spinal needle is left in place and additional drug is injected intermittently as needed

Complications of Spinal Anesthesia

FALL IN BLOOD PRESSURE A fall in blood pressure is fairly common following spinal anesthesia, due to the effect of the level of anesthesia in abolishing the vascular tone in the splanchnic region and in the lower extremities However, a drop in blood pressure during spinal anesthesia may also be related to traction on viscera and, as with any other anesthetic, to blood loss—in addition to various other causes (Table 14, p 361)

A fall in blood pressure due to reduced vasomotor tone in the lower one-half of the body can usually be treated satisfactorily

by elevating the lower extremities or by placing the patient in a Trendelenburg position If necessary, Neo-Synephrine or some other vasopressor drug may be given intravenously at a slow drip Shock due to hemorrhage should be treated with blood transfusion, not with vasoconstrictor agents

NAUSEA AND VOMITING Patients often become nauseated and vomit during spinal anesthesia, particularly following traction on the various organs of the upper abdomen such as the stomach Nausea may also signal the approach of shock.

POST SPINAL HEADACHE. It is now generally agreed that a major factor in the development of a persistent post spinal headache is the reduction of cerebrospinal fluid pressure Evidence in favor of this explanation includes the following [4]

1 Headache similar to "post-spinal" headache can be produced in man in the upright position by withdrawal of fluid and can be abolished by restoration of this fluid.

2 In many patients with postlumbar puncture headache, a second puncture will reveal either low pressures or pressures of approximately zero

3 Transient relief of postlumbar puncture headache by the subarachnoid injection of fluid may be achieved

4. The use of a very small bore needle reduces the incidence of the typical headache

SERIOUS NEUROLOGIC SEQUELAE. Among the various organic neurologic complications reported with spinal anesthesia are paraplegia, abducens paralysis and lesser degrees of extremity paralysis. However, in a follow up study of 10 098 spinal anesthetics in 8460 patients Dripps and Vandam[5] found no major neurologic sequelae.

Complications of Anesthesia in General

Respiratory Difficulties

Anoxia or hypoxia (Table 21) is the most serious consequence of respiratory inadequacy, and may result from a number of causes Among these are an overdose of preanesthetic sedative drug (particularly of morphine), an overdose of the anesthetic agent itself, the use of nitrous oxide without adequate amounts of oxygen, breath holding, laryngospasm, inadequate delivery of oxygen through the inspired air, anemia, shock, and other causes It is not uncommon for a patient to receive an overdose of morphine sulfate and to come to the operating room with a very slow respiratory rate (Fig 216) The fact that an overdose of the anesthetic agent can produce hypoxia due to inadequate respiratory efforts is of course well known Anoxia due to breath holding and laryngospasm does not usually result in tissue damage, though at the time the appearance of the patient may be quite disturbing.

Aspiration of gastric contents into the lungs is always a potential hazard and of course interferes, often fatally, with respiration. This is most likely to occur in patients who have gastric retention or intestinal obstruction, or in patients who have eaten recently the last is encountered most often in obstetric patients and in children. With children, it is advisable never to take the word of the mother or of the child that he has not eaten in the last 4 hours, for all too frequently the stomach will contain food It is better to delay operation a few hours, where possible. If the issue is then still in doubt, one can further protect the patient with the use of an endotracheal tube, or by gastric lavage Pulmonary aspiration or spillover is also a hazard when one is resecting a portion of the lung for abscess, bronchiectasis, or a large tuberculous cavity Such *spillover can produce* extensive and perhaps fatal pneumonitis in the remaining lung—not to mention subsequent spread of the infection if the patient survives the immediate operation. Finally no one who has performed a tonsillectomy in a child under open drop ether is likely to forget the possibility of the aspiration of blood!

Other Circulatory Disturbances

MARKED DIMINUTION IN BLOOD PRESSURE. Asphyxia may cause an initial *rise* in the arterial blood pressure, followed later by a

TABLE 21 HYPOXIA CLASSIFICATION BY CAUSE*

A Inadequate oxygenation of normal lungs
  1 Deficiency of oxygen in atmosphere, such as occurs during
    a Ascent to high altitudes where total gas pressure and hence oxygen pressure is subnormal
    b Exposure to an atmosphere at normal barometric pressure with an oxygen content below that of room air (for example, a 90 per cent nitrous oxide-10 per cent oxygen mixture)
  2 Obstruction to flow in pharyngeal or laryngeal airways caused by
    a Soft tissue relaxation in unconscious patients
    b Glottic and subglottic edema
    c Foreign bodies
    d Ludwig's angina
    e Carcinoma of larynx
    f Nerve or muscle paralysis
    g Spasm of vocal cords (laryngospasm, stridor)
  3 Obstruction to flow in tracheobronchial airway resulting from
    a External pressure
    b Foreign bodies
    c Bronchial constriction
    d Edema
    e Secretions
  4 Insufficiency of respiratory muscles caused by
    a Anterior poliomyelitis
    b Neuritis
    c Phrenic paralysis
    d Myasthenia gravis
    e Administration of curare-like drugs
    f Increased intracranial pressure
    g Injury to medulla oblongata
    h Excessive doses of anesthetic agents or other depressant drugs, such as morphine or barbiturates
    i Tight dressings
    j Abdominal distention
B Inadequate oxygenation of abnormal lungs
  1 Insufficient quantity of functioning lung tissue resulting from
    a Pneumothorax
    b Hydrothorax
    c Increased intra-abdominal pressure
    d Atelectasis
    e Pneumonia
    f Neoplasm
    g Cyst
    h Infarct
    i Tuberculous cavitation
    j Pulmonary hemangiomata
    k Removal of lung tissue
    l Congestive heart disease
    m Emphysema
  2 Improper alveolar mixing of inspired gases
  3 Poor diffusion of gases across alveolar capillary membrane caused by
    a Pulmonary infection with exudation into the alveoli
    b Pulmonary fibrosis
    c Diffuse pulmonary hemorrhage
    d Pulmonary capillary sclerosis
C Venous-arterial shunts—these may occur in
  1 Some types of congenital heart disease
  2 Pulmonary hemangiomata
  3 Cases in which blood is circulating through unaerated alveoli
D Inadequate transport of oxygen by the blood
  1 Diminution of active hemoglobin caused by
    a Severe, acute, or chronic anemia
    b Methemoglobinemia
    c Carbon monoxide poisoning
    d Sulfhemoglobinemia
  2 Deficient circulation
    a Generalized lack found in
      (1) Hemorrhage
      (2) Shock
    b Localized lack found in
      (1) Peripheral vascular disease
      (2) Peripheral vasoconstriction
      (3) Cardiac pathology
        (a) Congestive heart failure
        (b) Coronary occlusion
        (c) Acquired valvular defects
        (d) Congenital cardiac anomalies
E Inadequate tissue oxygenation
  1 Tissue edema
  2 Abnormally high tissue demand for oxygen
  3 Poisoning of cellular enzyme systems

Excessive doses of anesthetics and sedatives depress enzyme systems, cyanide inactivates cytochrome oxidase

* From AMERICAN MEDICAL ASSOCIATION *Fundamentals of Anesthesia*, Ed 3 Philadelphia, W B Saunders Company, 1954 (After Comroe, J H, Jr, and Dripps, R D)

rapid *fall* in blood pressure (Fig 217) The surgeon should always view with alarm the observation by the anesthetist that, though some blood has been lost, the blood pressure not only has not fallen, it is actually rising This is often a warning sign of anoxia or of hypercapnia, however, if at this point the pulmonary ventilation is increased by the anesthetist, the blood pressure may decline to normal levels and no shock ensues Even

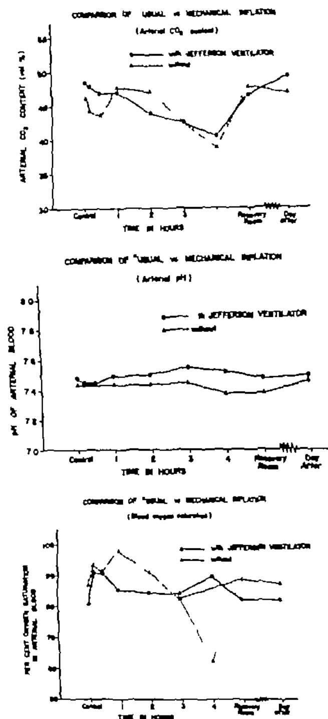


Fig 216 Comparison of "usual" *versus* mechanical inflation of the lungs during anesthesia. (From HARDY J D DAMPEER, J O JR TURNER, M D., AND BITTENBENDER, G Data published in Surgical Forum 7: 182 1957) Fifteen patients were studied with each method. Toward the end of operation hyperventilation occurred in both groups and lowered the CO_2 content of arterial blood In general, the blood pH was maintained satisfactorily by both methods. The control *arterial oxygen* saturations were depressed in the initial studies by the heavy preanesthetic medication then employed While the averages indicate that satisfactory ventilation can be achieved by either manual or mechanical assistance 2 patients in the "manual" group suffered serious hypoxia and respiratory acidosis, and one had a nonfatal cardiac arrest. Averages obscure such individual variations.

the fall in blood pressure which must eventually follow an initial rise due to serious anoxia may also be effectively treated by increasing the respiratory function, if anoxia has not existed too long Unfortunately, the initial and warning elevation of blood pressure in asphyxia may not occur if the patient is already quite deeply anesthetized This is particularly true if the third plane of the third stage has been reached.

The most common cause of hypotension during anesthesia is still, however, blood loss with inadequate blood replacement Other causes of shock during anesthesia are shown in Table 14 (p 361)

HYPERTENSION DURING ANESTHESIA Marked rises in blood pressure may be produced by epinephrine secretion incident to the struggles and emotional excitement of the induction of the anesthesia The blood pressure is usually higher during the earlier portions of the anesthetic induction than it is after the patient has reached the stage of surgical anesthesia.

An undiagnosed pheochromocytoma may, very rarely precipitate severe hypertension followed by circulatory collapse

Cardiac Standstill and Ventricular Fibrillation

Etiology Cardiac arrest and ventricular fibrillation are treated in much the same manner and therefore will be considered together

Cardiac standstill may occur from any of a number of factors, the most common of which is excessive anesthesia or asphyxia, or both, or from certain strong vagal stimuli such as may occur when one is producing *traction* in the region of the pulmonary hilum Of course, cardiac arrest is particularly likely to occur during heart operations.

Ventricular fibrillation on the other hand, may follow any of the causes which have been enumerated for cardiac arrest but it also apparently can occur in situations in

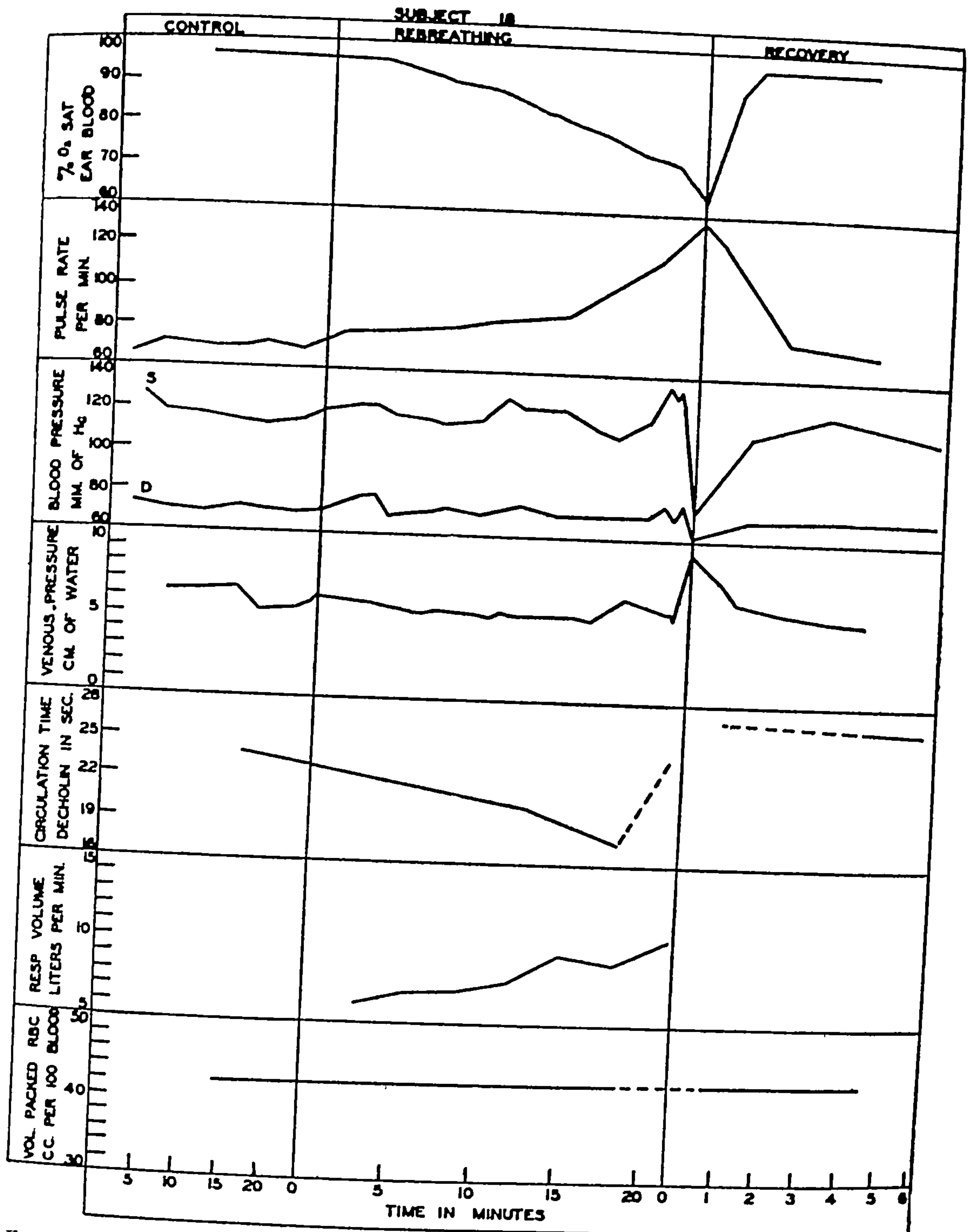


Fig 217 Circulatory alterations produced by rebreathing in man (From ERSHLER, I, KOSSMANN, C E, AND WHITE, M S Venous pressure and circulation time during acute progressive anoxia in man Am J Physiol, **138:** 595, 1942–1943) The subject was allowed to rebreathe without the addition of oxygen to the gas mixture Eventually the oxygen available in the system was so depleted that the oxygen concentration in ear blood fell to 65 per cent, pulse rate approached 140, blood pressure fell to 80 systolic after a brief preliminary elevation, and venous pressure rose, as did the minute respiratory volume These experimental findings in a volunteer subject are very similar to those observed during hypoxic anesthesia

which serious hypoxia has not occurred and where the anesthesia is actually very light The presence of epinephrine in the blood may increase the general irritability of the heart, as does cyclopropane

Nevertheless, cardiac standstill is far more frequent than is ventricular fibrillation, aside from cardiac operations, and the most common cause is that of anoxia or hypercapnia due to any of several causes

The following case report illustrates the type of anesthetic conduct which can produce cardiac arrest

Case study Patient H. B was a 47 year-old white woman who was in good health with the exception that she had chronic cholecystitis with cholelithiasis She was brought to the operating room following preanesthetic medication which consisted of morphine sulfate, 10 mg, and atropine sulfate, 0 4 mg, given subcutaneously 1 hour previously The patient was a moderately obese individual with a short neck, and the student anesthetist experienced difficulty in ventilating the lungs adequately before any attempt was made to introduce the endotracheal tube However after some effort an endotracheal tube was inserted and the face mask was reapplied. At this point the surgeon had finished scrubbing and had entered the operating room where the anesthesia was being induced. As he was putting on his gown and gloves he noted that the patient's respiratory excursions were very slight and that the movements of the gas bag were also very slight, though the patient was obviously "pulling" very hard in an effort to inspire. The skin was cyanotic, but was not deeply so, and no interference with the conduct of the anesthesia was attempted. Nevertheless, it was quite obvious that the induction was not proceeding smoothly and so the surgeon "broke scrub" and placed a finger upon the radial artery The pulse was quite rapid and presently it began to couple that is, there were two beats and then a dropped third beat and this continued as the patient became more and more cyanotic At this point the surgeon insisted that the student call her superior and this was done The superior immediately seized the syringe containing Pentothal to give the patient additional dose intravenously "to relieve the spasm." This the surgeon discouraged He asked that, instead the mask be removed and the endotracheal tube be examined—since the chest was not being expanded even with forceful manual compression of the gas bag. It was found that the endotracheal tube was completely kinked in the upper pharynx and that gas could not be forced through it. The patient by this time was deeply cyanotic and the pulse was extremely irregular and weak. However, after another endotracheal tube had been inserted and effective respiration achieved, the skin color soon improved. The pulse remained irregular for a few more minutes until a number of adequate respirations had been accomplished, but it then gradually returned to one of moderate rate, good volume, and regular rhythm

At this point a consultation was held between the surgeon and the anesthetist and it was decided to continue the operation since now the blood pressure and the respiratory exchange appeared to be satisfactory The operation began with a right subcostal incision which was developed to expose the peritoneal cavity and the gallbladder However, no sooner had a clamp been placed upon the gallbladder than the anesthetist stated that the pulse was no longer palpable The surgeon quickly palpated the aorta and there was no pulsation Accordingly, the left chest was immediately entered just below the large pendulous breast and the heart was found to be at a standstill Manual compression for only three times was sufficient to start the heart again, and thereafter it continued to beat adequately Presently the chest was closed The gallbladder was then quickly removed and the abdomen was closed. The patient made an uneventful recovery

Comment This patient is illustrative of numerous problems which enter into the cause and management of cardiac arrest. The cardiac musculature had already been depressed by the period of asphyxiation which had occurred during the time that the kinked endotracheal tube remained in the trachea largely blocking the respiratory exchange The fact that the cardiac neuromuscular mechanism was affected was reflected in the fact that the pulse had become markedly irregular and faint during that time

Subsequently, the operation was continued because it was considered that the anesthesia was now satisfactory, which it was Nevertheless, the prolonged period of decreased oxygen saturation had rendered the cardiac musculature abnormal in its reaction, the traction on the gallbladder—perhaps associated with some fall in blood pressure (the blood pressure did not happen to be measured at this particular time) and the fact that the reflexes set up in this region affect the heart—resulted in cardiac standstill Fortunately, the anesthetist was now thoroughly alert to any further difficulty, and she had her hand upon the pulse The state of cardiac arrest was noted almost the instant it occurred, and this permitted prompt left thoracotomy and cardiac massage which quickly restored the cardiac beat The longer the delay, the more difficult it is to start the heart

THE MANAGEMENT OF CARDIAC ARREST The management of cardiac arrest must begin long before the surgeon is ever face to face with this dire emergency in the operating room Surgical residents and all others doing surgery, regardless of what type of surgery it is, must now indoctrinate themselves with the measures which must be taken when cardiac arrest occurs They must steel their conviction that they will promptly open the chest, if no pulse or blood pressure can be obtained when these were previously present The importance of the development of a definite plan of action to be used when one is confronted with cardiac arrest cannot be overemphasized We are reminded of a young resident who was faced with the necessity of doing a tracheotomy immediately for postoperative thyroid bleeding, instead of meeting the emergency, he rushed to the operating room to find an anesthetist who would do an endotracheal intubation But while he was gone the patient died The resident's self-analysis was an honest and searching one He stated that when next aware of the need for definite and immediate action he would not again fail to meet the issue squarely himself And he proved this the following week He was doing an abdominal operation in a poor risk patient when cardiac arrest occurred Without the slightest hesitation he opened the chest, restored the heart beat, and saved the patient's life

When the anesthetist states that the pulse is no longer palpable and the blood pressure is zero, the surgeon must assume that cardiac arrest exists—if he too can feel no pulse in a major vessel or if a cardioscope (if being used) so indicates The matter of opening the chest is now such a simple one that there can be no excuse for failure to attempt resuscitation *Three things must be done First, the chest must be opened and the heart massaged at a rate of from 60 to 120 beats per minute* (Fig 218) *Second, the anesthetist must vigorously inflate the lungs by use of the bag at a rate of at least 20 respirations per minute* (Fig 219) *Third, just as quickly as possible an intravenous infusion must be started, preferably with blood, but with plasma, plasma expander, saline or glucose, if blood is not available*

These three measures provide for the immediate emergency If the ventricles are fibrillating, the arrhythmia can be managed with electroshock after the patient and the heart itself have been reoxygenated Prolonged massage may be required (hearts have resumed function even after several hours), but usually the beat is rapidly restored if the duration of arrest has been brief

The surgeon is often worried by several largely academic problems For example, he is apprehensive that bleeding from the intercostal arteries will occur This obviously will not be serious, since if the heart has stopped there will be only the static blood pressure in these vessels Too, there is the fear that the lung will be cut Even if this does occur—though it rarely will occur if even the most nominal care is used—it does not constitute a serious injury, the defect can be readily oversewn with chromic catgut later Also, there is the possibility that the heart itself will be stabbed with the

knife as the chest wall is opened We have actually seen this occur in one patient, the knife used to open the chest actually inflected a small stab wound in the left ventricle However, the coronary artery was not cut, the heart was started by manual compression the stab wound was oversewn, and the resident could credit himself with the saving of a life Of course, chest wall bleeding will occur after the blood pressure has been restored but the vessels are easily ligated

The importance of having the right heart

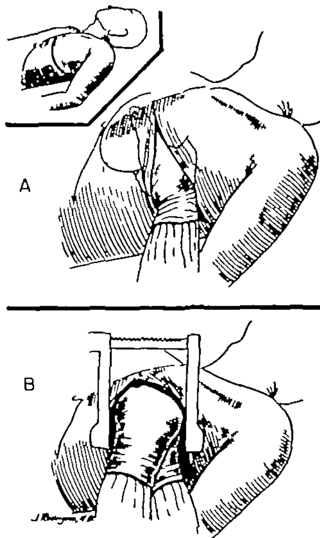


Fig 218 The important thing in cardiac arrest is to open the left chest quickly and begin compressing the heart. The lungs are ventilated effectively with air or pure oxygen and intravenous fluids are given (preferably blood plasma or plasma expander) Other details must await these three basic requirements.

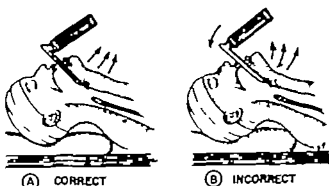


Fig 210 All surgeons should be thoroughly versed in the use of the laryngoscope (After Adriani.)

fill as it is being compressed is a very real one The heart will not be filling if the venous return to the right heart is inadequate and instead of an effective pulse at a rate of from 60 to 100 times per minute, a slower rate will have to be adopted to permit the heart to fill with blood However, with the infusion of a suitable fluid intravenously the venous return to the right heart will be adequate

MANAGEMENT OF VENTRICULAR FIBRILLATION Ventricular fibrillation poses a more serious problem than does simple cardiac standstill. Nevertheless, as noted, the *initial* treatment for ventricular fibrillation is the same as that for cardiac standstill. Cardiac massage, intravenous infusion, and pulmonary ventilation with pure oxygen are maintained for several minutes before an attempt is made to bring the fibrillating ventricles to a standstill after which the treatment is again precisely the same as for cardiac standstill So, to produce a regular rhythm in the presence of ventricular fibrillation, it is necessary first to stop the purposeless muscular contractions entirely This may be accomplished in one of two ways One may cross-clamp the aorta just distal to the coronary arteries and instill 2 per cent potassium chloride into the aorta proximal to the occluding clamp this fluid is then massaged into the coronary arteries and the heart comes usually, to a standstill. On the other hand one may use the electroshock

apparatus (defibrillator)—which we prefer Many such instruments are now available commercially

It is often stated that no more than 5 minutes must have elapsed before effective heart beat is restored, else the brain will have been damaged beyond recovery Unfortunately, the time available is often even shorter than 5 minutes, for a relative anoxia may have existed for some time to cause the cardiac arrest

REACTIONS TO LOCAL (INCLUDING TOPICAL) ANESTHETIC AGENTS Adriani and Campbell[2] have recently reported the very rapid absorption of local anesthetics through mucous membranes For example, a quantity of a drug that resulted in no detectable blood level when infiltrated subcutaneously gave levels when applied topically that were equal to one-third to one-half of those after intravenous injection Thus, reactions caused by local anesthetic agents are probably due to overdosage with absorption Accordingly, the less drug used, the less will be the incidence of reactions—as has been noted by all who do bronchosc[illegible] regularly

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Chapter 18

The Endocrine System

The Pituitary

If it performed no functions other than to regulate the rates of thyroid and adrenocortical activity, the pituitary would deserve consideration in this volume However this gland of manifold secretions has many other far reaching potentialities Certain of these will be reviewed, and the physiologic effects of hypophysectomy and of pituitary tumors will be outlined.

The Anterior Pituitary

SURVEY OF HORMONES (FIG 220) The anterior lobe of the pituitary consists of at least three types of cells—the acidophil, the basophil, and the chromophobe (nonfunctioning?) cells. The following hormonal substances are secreted (1) adrenocorticotropic hormone (ACTH) (2) thyroid stimulating hormone (TSH), (3) growth (somatotropic) hormone, (4) gonadotropic hormone (gonadotropin), and (5) lactogenic hormone (prolactin)

Adrenocorticotropin (ACTH) It was noted in Chapter 1 that the activity of the adrenal cortex is regulated almost entirely by the release of ACTH (a protein substance) by the pituitary In turn the rate of release of this substance by the pituitary is related to the level of adrenocortical hormones in the blood. For example, the administration of cortisone or hydrocortisone suppresses the secretion of ACTH by the patient's own pituitary (Fig. 242) Conversely adrenocortical insufficiency may be associated with an increased blood ACTH level if the cortical insufficiency is not secondary to pituitary disease

ACTH stimulates the adrenal cortex to secrete increased amounts of hydrocortisone, corticosterone, aldosterone (?) and, presumably, other adrenocortical hormones Moreover, the physiologic effects of ACTH appear to be mediated entirely through the adrenocortical hormones. The material is inactive by the oral route, readily effective by the intramuscular route, and maximally effective by the intravenous route

Thyroid stimulating hormone (thyrotropin, TSH) This tropic material increases thyroid weight and activity in much the same fashion that ACTH influences the adrenal cortex, its absence results in thyroid regression. Administration of TSH to normal animals produces an increase in thyroid weight, a loss of colloid with an increase in acinar cell height, an increased uptake of I^{131}, an increase in the serum protein bound iodine (PBI) level, and an elevation of the basal metabolic rate (BMR)

Diffuse toxic (exophthalmic) goiter or Graves' disease has been considered to be due to an increased rate of release of TSH, though Werner[103] has presented evidence that the fault is primary in the thyroid. The solitary toxic nodule is considered perhaps to reflect localized hypersensitivity to the normal amount of TSH. This material is effective by the parenteral but not by the oral route

Growth hormone (somatotropin) This substance has been obtained in purified form from the pituitaries of cows and hogs and

THE ANTERIOR PITUITARY HORMONES AND THEIR FUNCTIONS

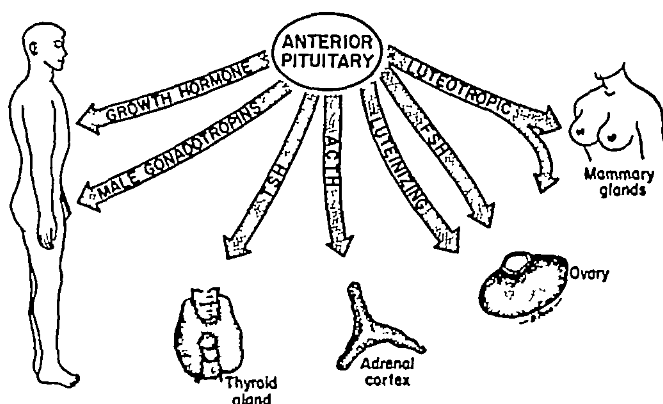


Fig 220 The pituitary hormones have far reaching effects

has been extensively studied by Evans, Simpson, and Li[44] and by several surgical units in recent years It normally stimulates growth in the young organism, and the tissue formation so stimulated is high in protein and low in fat A positive nitrogen balance has been achieved in adults following the administration of growth hormone

If one injects growth hormone in young dogs, changes are produced in the skeleton which resemble acromegaly Presumably growth hormone, which affects all substances necessary for normal lean tissue construction, is responsible for the excessive growth in the adolescent that may result in gigantism

Possible clinical uses of the purified material have not been clearly defined Its use in the management of burn patients has not materially influenced the mortality

Gonadotropic hormone (gonadotropin) This term embraces both the follicle stimulating hormone (FSH) and the luteinizing hormone (LH) The ovary responds to the gonadotropic substances with growth of the primordial follicle, ovulation, and formation of the corpus luteum Moreover, steroid hormones which influence the growth and development of the endometrium, as well as the secondary sex organs and characteristics, are produced by the ovary in response to gonadotropins The corpus luteum is maintained by prolactin or luteotropin In the male, FSH may promote spermatogenesis while LH stimulates the Leydig cells which secrete androgenic steroid

Other hormones of the anterior pituitary It is by no means certain that all major hormones of the anterior pituitary have been discovered For instance, it has always seemed odd that such important endocrine organs as the parathyroids, pancreas, and adrenal medulla should not be more directly influenced by the pituitary tropic substances than we have sure knowledge of at present

HYPOFUNCTION OF THE ANTERIOR PITUITARY

Spontaneous hypopituitarism Since the major function of the anterior pituitary is to secrete the important tropic hormones which regulate the activity of various other endocrine organs and of general somatic development, serious consequences follow diminished pituitary activity In 1914 Simmonds[97] described a man with clinical findings suggestive of hypopituitarism, and autopsy studies revealed that the essential feature was destruction of the pituitary gland The primary endocrine defect had been insufficiency of the hormones ordinarily elaborated by the anterior lobe of the pituitary Hypopituitarism has since become commonly recognized, and some of the lesions which produce this hypofunction are tumors, cysts, gumma, massive tuberculous necrosis, granulomas of unknown etiology, hypophysectomy, and Sheehan's postpartum necrosis of the anterior lobe Sheehan[98] described massive focal atrophy of the anterior pituitary that occurs only in women and is nearly always of postpartum origin The lesion appears to represent an ischemic necrosis similar in type to an infarct and occupying most of the anterior lobe He reported 14 cases of fresh pituitary necrosis and 1 of late pituitary necrosis observed in the course of 2 years at the Glasgow Royal Maternity and Women's Hospital It is considered that the necrosis occurs in the hypertrophied pituitary of pregnancy due to hemorrhage and, perhaps in addition, because of hypotension or general circulatory collapse at the time of delivery, resulting in

inadequate blood flow to the pituitary for a short time. The treatment of this condition with replacement therapy has thus far been disappointing.

Surgical hypopituitarism (hypophysectomy for advanced cancer) [11] The use of hypophysectomy in the treatment of advanced breast cancer in 28 patients was reviewed by Kennedy, French, and Peyton.[63] In discussing the endocrinologic aspects of this procedure, they pointed out that the best available index in the living subject of the completeness of hypophysectomy, even though a crude one, is the subsequent activity of endocrine organs dependent upon the pituitary tropic stimulus. In their patients the best sign of marked hypopituitarism was the inability to withdraw cortisone therapy, for to do so resulted in the usual evidence of *acute adrenocortical insufficiency* consisting of hypotension, fever, and collapse. (More recently LeRoy *et al* have used tagged cholesterol and measured corticoid production.[64])

Ovarian function could not be studied in most patients because oophorectomy had been performed prior to the hypophysectomy, nevertheless, measurement of the pituitary gonadotropic hormone revealed a disappearance of this substance after operation and in no case did it reappear in the urine.

Thyroid function varied following hypophysectomy Often within 3 months of operation the patients noted dry skin, decreased sweating, cold intolerance constipation, weight gain, and poor regrowth of scalp hair Subsequently, sluggish behavior, myxedematous facies and a slow response of tendon reflexes was observed Thyroid function tests revealed a decrease to hypothyroid levels

Diabetes insipidus of some degree appeared in virtually every patient, the degree of polyuria and polydipsia varying in different subjects. In some the condition was temporary and in others permanent. Whether or not it was permanent appeared to be related not to the completeness of hypophysectomy but to whether or not there was irreversable damage to the cells of the hypophyseal stalk and hypothalamus. Polyuria was controlled, where required by nasal insufflation of pitressin powder

The advanced *breast cancer* for which the operation had been performed was considered to be objectively improved in 18 of 28 patients treated. Even so, hypophysectomy constitutes a rather heroic measure for brief palliation.

TUMORS OF THE ANTERIOR PITUITARY *Eosinophil (acidophilic) adenomas of the anterior pituitary* comprise approximately 20 per cent of pituitary adenomas, and they secrete abnormal amounts of various of the anterior pituitary hormones When the acidophilic adenoma arises in pre-adult life before ossification is complete, *gigantism* results. If the tumor develops in an adult, the condition known as *acromegaly* may be produced it is characterized by overgrowth of the bones of the hands, feet and face, atrophy of the gonads with decline in sexual function (this may be preceded by a temporary increase in sexual function), enlargement of the viscera, stimulation of the thyroid and adrenals which may result in signs of excessive activity of these organs, and, finally, derangements in glucose metabolism, probably secondary to the increased adrenocortical activity Visual field defects may result from optic nerve involvement.

Basophil adenomas of the anterior pituitary [11] rarely grow to sufficient size to cause pressure symptoms. For many years following Cushing's original description of the basophil adenoma it was considered that the tumor of the pituitary was the cause of Cushing's syndrome or, at least, that Cushing's syndrome (p 565) arose from overstimulation of the adrenal cortices by some secretion of these basophil cells, presumably ACTH. Nevertheless, recently there has been doubt whether these basophil tumors are responsible for any aspect of Cushing's syndrome In fact there is evidence that the "neoplastic" changes in the basophil cells may be the result of the in

creased blood level of adrenocortical hormone, in other words, that the basophil tumor may be a result rather than the cause of the Cushing's syndrome, at least in some instances Moreover, many believe that ACTH is secreted, not by the basophil cells, but by the eosinophil cells of the anterior pituitary Therefore, the significance of basophil tumors is uncertain at this point

Chromophobe adenomas constitute about 70 per cent of the pituitary adenomas, and are by far the largest group of pituitary tumors requiring surgical intervention No hypersecretion has been attributed to them and, as a rule, the symptoms of chromophobe tumors are largely those of hypopituitarism, due to encroachment upon and destruction of the endocrine cells of the anterior lobe As indicated above, hypopituitarism is characterized by the loss of libido in the male and amenorrhea in the female Body hair becomes scant and men need shave only rarely The basal metabolic rate is usually diminished and obesity may occur

Other tumors of the pituitary are adamantinomas and suprasellar cysts, neither of which has any particular physiologic significance other than that it may compress neighboring structures

Differential Diagnosis of Pituitary Tumors The well developed clinical picture of acromegaly or giantism is usually enough to permit a diagnosis of eosinophil adenoma Patients with these tumors often have severe headaches, but as a rule visual disturbances due to compression of the optic chiasm or optic nerves do not occur until late The visual field defect, when it occurs, is usually that of bitemporal hemianopsia or a right or left homonymous hemianopsia

Patients with eosinophil adenomas may eventually exhibit signs of decreased pituitary function Roentgen examination may reveal enlargement or erosion of the sella turcica and surrounding structures

Management of Pituitary Tumors The eosinophil adenoma has in the past most commonly been treated initially with deep roentgen therapy If this has no effect and the tumor progresses, as evidenced by an increasing defect in visual fields and headache, surgical intervention is indicated It may not be possible to remove the entire tumor, but the optic chiasm must be freed from pressure

At the present time, neurosurgeons are more and more attacking the pituitary directly, with irradiation being depended upon less often Surgical approaches and technics have been better worked out, and the operation does not carry the same risk as it previously did Certainly surgery is usually employed for the management of chromophobe adenomas, the most common pituitary tumor The most serious effect of many pituitary tumors is that of visual loss, and they should be dealt with before vision has become seriously impaired

The Posterior Pituitary

The posterior lobe or neurohypophysis is anatomically fused with, but physiologically separate from, the anterior lobe or adenohypophysis It is intimately connected with the hypothalamus and it secretes two hormones the antidiuretic substance (ADH, pitressin) and the oxytocic substance (pitocin) The latter stimulates the uterus, particularly at term, and it has also been shown to promote the discharge of milk from the breast during lactation [85]

Hypofunction of the neurohypophysis results in diabetes insipidus (p 42), characterized by the secretion of large quantities of dilute urine, necessarily accompanied by polydipsia The condition is managed with pitressin

Hyperfunction of the neurohypophysis, such as might be produced by a functioning tumor, has not been described, to our knowledge

The Thyroid

Embryology The thyroid gland develops as an invagination of the floor of the embryonic pharynx This process descends as a cellular stalk to the anterior part of the neck

and then, by proliferation of its cells, gives rise to the epithelial elements which are later to become the adult organ. The connection with the pharynx, known as the thyroglossal tract usually disappears and is represented only by the foramen cecum at the base of the tongue If this structure does persist, it may give rise to the familiar thyroglossal duct cyst. The normal adult thyroid gland weighs from 24 to 30 gm.

The gross anatomic relationships of the normal thyroid are shown in Fig. 221 At operation certain complications are likely to arise if particular care is not exercised. First the recurrent laryngeal nerves ascend on either side of the trachea and run beneath the respective thyroid lobes The incidence of nerve injury at operation is probably in the neighborhood of 3 per cent or higher considering United States surgery as a whole Second the parathyroid glands may be inadvertently removed if a radical thyroidectomy is to be performed Third the thyroid gland has a rich blood supply and postoperative bleeding within the fascial confines of the neck can cause tracheal compression and asphyxia.

The Iodine Cycle: Rôle in Histologic Appearance of the Gland

Microscopically the organ consists of many spherical or oval follicles which are lined by cuboidal epithelium. The center or cavity of the follicles is normally filled with a pink staining viscid material known as the colloid of the gland, and it consists chiefly of an iodine-containing protein called *thyroglobulin* The colloid is decreased in amount in the hyperplastic or toxic gland, and the cells are more nearly columnar than cuboidal However, when iodine is given the patient whose gland is hyperplastic the colloid increases, the cells lining the follicles again become cuboidal and the appearance of the gland resumes the normal appearance

IODINE METABOLISM.[19, 81] Clearly the iodine cycle has much to do with the microscopic picture and the functional status of the thyroid gland What are some of the

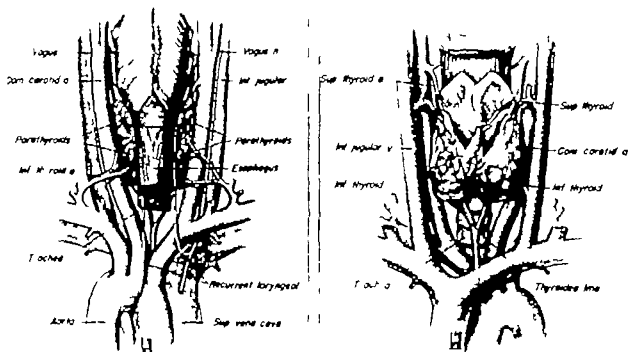


Fig 221 Posterior and anterior views of the thyroid and its relationships. (From HARDY J D *Surgery and the Endocrine System* Philadelphia, W B Saunders Company 1952)

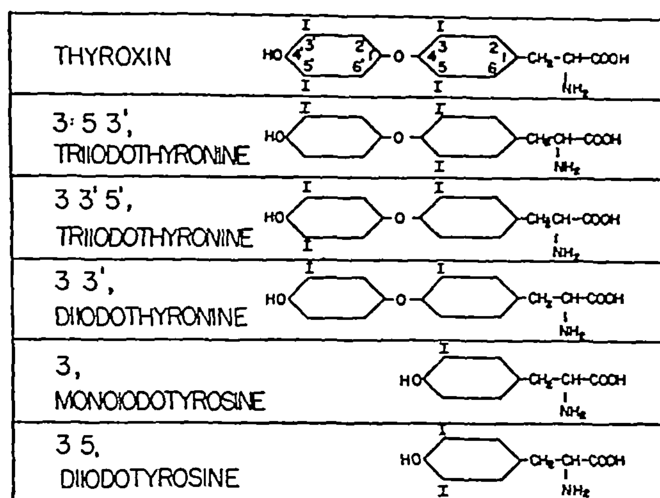


Fig 222 Structural formulas of iodinated amino acids found in the thyroid gland and in plasma (From OLINER, L In *Physiologic Principles of Surgery*, edited by L M Zimmerman and R Levine Philadelphia, W B Saunders Company, 1957)

more important aspects of the iodine cycle, particularly as regards the effect of various therapeutic measures?

The weight of iodine in the thyroid gland is approximately 15 mg , and this represents almost one-fifth of the total body iodine It is found in several known forms, and others will doubtless be described (Fig 222) Reports vary as to the exact proportions to be assigned the different forms in which elemental iodine is found in the thyroid gland and in plasma Roughly, in the gland inorganic iodide has been estimated at 10 per cent, thyroxine, 35 per cent, 3 5 3′ triiodothyronine, 20 per cent, diiodotyrosine, 25 per cent, monoiodotyrosine, 17 per cent, and monoiodohistidine, 2 per cent [86] It was only a few years ago that thyroxine was the only known active thyroid principle

It was seen above that the follicles of the normal thyroid gland contain considerable amounts of colloid (essentially thyroglobulin) This protein contains both thyroxine and diiodotyrosine, bound to the rest of the protein molecule by the peptide linkage Thus, thyroglobulin is a storage form of thyroxine Diiodotyrosine is a precursor of the latter, and monoiodotyrosine may be a precursor of triiodothyronine

The *iodine cycle* is presented in Figure 223 Iodide is extracted from the blood and concentrated in the thyroid gland at a level several hundred times that in the blood. It is excreted principally by the kidney However, iodide as such is not reactive with proteins to form the organic thyroid principles Therefore, some process must exist by which the iodide that the thyroid "traps" from the extrathyroidal iodide "pool" is oxidized to iodine This is emphasized by the demonstration of Dvoskin[42] that the subcutaneous injection of elemental iodine (I_2) can excrete a thyroxine-like effect on adrenal size and growth in thyroidectomized animals, while similar doses of iodide are virtually without effect There is evidence that this oxidation of iodide to iodine in the thyroid is catalyzed by a peroxidase, but Roche, Lissitzky, and Michel[93] do not consider that the presence of a specific oxidase is physiologically necessary for this reaction Regardless of whether or not a specific enzyme is required, it appears that *the effect of antithyroid drugs is to block the essential step of the conversion of iodide to iodine in the thyroid* In other words, following the administration of thiouracil the gland can still "trap" iodide from the blood stream, but it cannot convert it to iodine so that it can be incorporated with amino acids such as tyrosine to form thyroxine and other metabolically active thyroid principles

For the release of thyroxine into the blood stream the huge thyroglobulin molecule must be degraded, since it cannot itself normally pass into the capillaries This is effected by a proteolytic enzyme capable of liberating iodinated amino acids from the thyroglobulin The injection of thyrotropin (TSH) apparently activates this process, and the plasma thyroxine level rises

THYROXINE AND TRIIODOTHYRONINE To recapitulate, in the thyroid inorganic iodide is changed to iodine by peroxidase and is bound initially into monoiodotyrosine and diiodotyrosine (Fig 223) Two molecules of the latter are then combined to form thyroxine Triiodothyronine is also formed, perhaps by a coupling of monoiodotyrosine and diiodotyrosine or by a deiodination of thy-

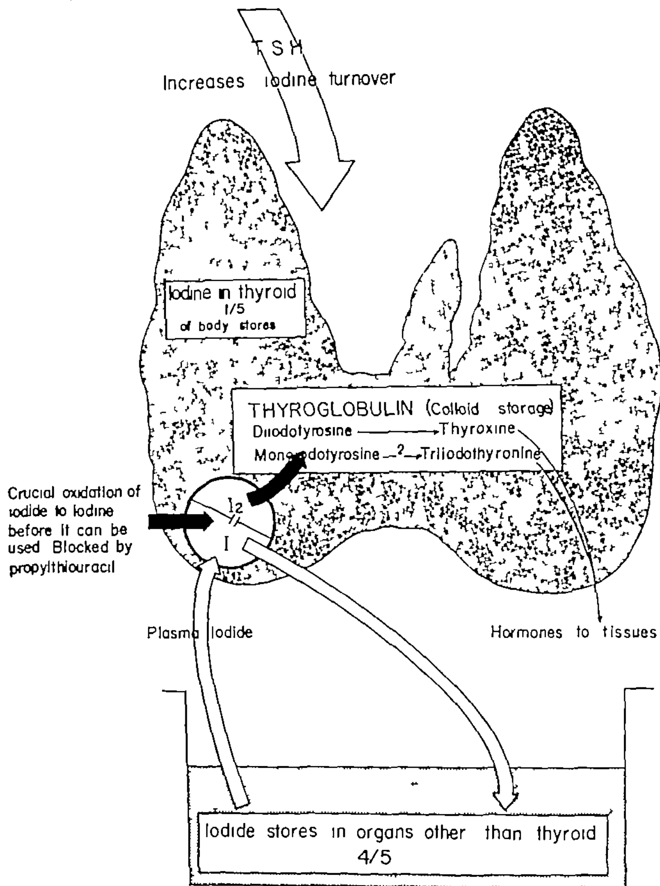


Fig 223 Thyroid function is intimately associated with iodine metabolism.

roxine. These and other iodinated amino acids, which represent the active thyroid hormones, are then stored in thyroglobulin, the familiar thyroid colloid material. Under proper stimulus, presumably that of TSH under usual circumstances, a proteolytic enzyme degrades the large thyroglobulin molecule and releases the various iodinated amino acids, but normally only metabolically active compounds reach the blood stream. To be active, the compound must carry iodine at the 3, 3′ position on the thyronine structure (Fig. 222).[86]

Since the rate of thyroid activity is normally controlled largely by the anterior pituitary (TSH), what regulates the release of thyrotropin? The level of circulating thyroxine appears to have some rôle, and the hypothalamus may contribute an additional effect.

By the use of paper chromatography it has been shown that only thyroxine and triiodothyronine are normally present in the plasma, the latter only in minute amounts in the absence of hyperthyroidism. Following surgical trauma or radiation damage, however, even thyroglobulin itself may appear in the circulation.

The general *metabolic effects of thyroxine* are well known. An initial effect is to increase the metabolic rate, but normal growth and mental development also depend upon an adequate supply of the thyroid hormones. Hypothyroidism during the growth period results in cretinism. Hypothyroidism in adults results in myxedema, characterized by abnormal collections of water, salt, and protein; these are promptly mobilized by the administration of active thyroid hormones. Other metabolic effects have to do with the metabolism of carbohydrate (deranged glucose tolerance curve and glycosuria, in thyrotoxicosis), of lipids (increased serum cholesterol level in hypothyroidism), and proteins (abnormal protein deposits in myxedema). The neuromuscular system exhibits evidence of increased irritability in the presence of excessive amounts of thyroxine, but eventually the muscles may exhibit actual atrophy and marked myasthenia. Auricular fibrillation and heart failure may accompany thyrotoxicosis of long standing, and there is evidence that the myocardium is more sensitive to thyroxine than are most other tissues. The thyroid hormone increases protein breakdown and results in a negative nitrogen balance if the patient does not eat with an increased appetite. Creatinuria is characteristic of hyperthyroidism and has been used as a means of diagnosing this condition; the response of creatinuria to the administration of thiourea has also been used as a test for thyrotoxicosis. Thyroxine increases rates of absorption from the gastrointestinal tract and is thought to diminish the secretion of TSH by the anterior pituitary. The relationship between thyroid and adrenal hormones will be referred to subsequently.

There is some evidence that thyroxine is converted to triiodothyronine at the tissue level before it is metabolically effective.

The *metabolic effects of triiodothyronine*[5] are qualitatively very similar to those of thyroxine, but quantitatively the former is more potent on a weight basis and produces physiologic effects much more rapidly. For example, McGavack and Reckendorf[77] compared the activities of desiccated thyroid substance, sodium L-thyroxine, and D,L-triiodothyronine in 12 cases of adult myxedema. The average daily control dose for desiccated thyroid was 152.6 mg. (range, 120 to 210 mg.), that for sodium L-thyroxine was 258.0 micrograms (range, 200 to 350 micrograms), and that for D,L-triiodothyronine was 145.1 micrograms (range, 100 to 175 micrograms). Moreover, the number of days required to bring the subject back to the euthyroid state with optimal doses of the respective drugs was, for desiccated thyroid 21.0, for sodium L-thyroxine 19.2, and for D,L-triiodothyronine 5.0, with individual variations.

Actually, the physiologic effects of triiodothyronine can be detected within hours following injection, while those of thyroxine require several days. This is of particular

interest in view of the fact it has been difficult to explain early postoperative nitrogen wastage on a thyroid basis, if thyroxine were the only thyroid hormone concerned However the early postoperative nitrogen wastage could be produced by the more rapidly acting triiodothyronine, though such an increase in this hormone has yet to be demonstrated conclusively

Mechanism of Action of Thyroid Hormones

It would appear that the thyroid hormones exert their influence upon tissue metabolism through a regulation of various enzyme activities Nevertheless, there is still no clear choice between the two principal possibilities as to the mechanism Direct participation of the thyroxine as a sort of coenzyme, or indirect release of metabolically active substances [11] Direct involvement of thyroxine in an enzyme system has never been established, but it has been suggested that thyroxine causes a release of coenzymes, protein carriers, or other substances needed for many of the energy transforming processes in all cells. It is also considered possible that thyroxine has different effects in different tissues. Thyroxine may influence tissue utilization of oxygen through an effect on cytochrome

Hyperthyroidism

PATHOPHYSIOLOGY Despite its prevalence and consequent intensive investigation, the specific mechanism by which spontaneous hyperthyroidism develops is still unknown Basically of course a derangement in the intrathyroidal metabolism of iodine results in the release of excessive amounts of thyroxine into the blood stream, presumably because of an inability to store iodine in the form of colloid (thyroglobulin) This results in an even greater rate of uptake of inorganic iodine (iodide) with further oxidation of the iodide by peroxidase to produce more substrate for thyroxine synthesis and release.

Toxic diffuse goiter versus toxic nodular goiter (different diseases?) While the ultimate effects of all forms of hyperthyroidism—factitial, hyperpituitarism as in acromegaly, Graves disease, and toxic adenoma —are largely due to excessive blood and tissue levels of active thyroid principles, there are wide variations in the clinical pictures which accompany these conditions especially between that of diffuse toxic or exophthalmic goiter (Graves disease) and nodular toxic goiter Perhaps the most striking difference is the exophthalmos which usually occurs in Graves' disease, but many believe that there is a fundamentally different stimulus for the increased activity Specifically it has been assumed that Graves disease is probably due to an increased secretion of TSH by the pituitary, while the toxic nodule is due to a primary defect within the thyroid gland itself It has been suggested that cells of the toxic nodule are hypersensitive to the normal amount of thyrotropin. Unfortunately, the matter is probably not to be so neatly settled Werner and his associates,[103] for example offered evidence that Graves disease is not a form of hyperpituitarism but that it too arises from a fault that is primary in the thyroid itself They noted that whereas in normal subjects the administration of thyroxine or triiodothyronine would reduce the thyroid uptake of I^{131} (by suppressing TSH secretion) this effect was not observed in Graves' disease

Dobyns[40] reviewed the physiologic concepts in Graves' disease, including the possible influence of the higher nervous centers in the (emotional) genesis of this condition He made the important point that the concept of the disease has been broadened to take account of the fact that initially there may be thyrotoxicosis without exophthalmos or exophthalmos without goiter Later thyrotoxicosis, exophthalmos, and diffuse goiter may all three be manifest (Fig 224) Another point particularly emphasized was that the approximate date of onset of Graves' disease, especially in young individuals, is usually fairly well defined, in contrast to the insidious onset of symptoms



Fig 224 Graves' disease exophthalmos, hyperthyroidism, and diffuse goiter It is widely believed that this disease is due to excessive secretion of thyroid-stimulating hormone (TSH), and emotional overtones are prominent in both the pathogenesis and in the established disease itself

in toxic nodular goiter Moreover, many years often elapse from the time that a nodular goiter is noted until the onset of symptoms of hyperthyroidism Thus, toxic diffuse goiter and toxic nodular goiter vary as to general behavior, toxic nodular goiter is virtually never associated with exophthalmos, and the response to iodine is different Patients with Graves' disease are notoriously emotionally unstable and excitable, as compared to the calm or even "apathetic" individual with toxic nodular goiter Toxic diffuse goiter responds within a few days to iodine therapy, in contrast to the less dramatic response of toxic nodular goiter This same general type of response of the two types of goiters is also encountered in radioiodine therapy

Exophthalmos The mechanism of the exophthalmos of Graves' disease remains unsettled Dobyns[10] obtained evidence that the anterior pituitary produced not only TSH but also a separate exophthalmos producing substance (EPS) which would selectively produce exophthalmos in the Fundulus, a small minnow However, this work awaits further confirmation

The treatment or control of exophthalmos is unsatisfactory, due in part to the fact that the etiology remains in doubt Dobyns has pointed out that the instances of "exophthalmos" should be separated in two groups the first group consists of those cases encountered in Graves' disease which are not associated with actual forward displacement of the globe (in contradistinction to lid signs) and which subside when the hyperthyroidism is controlled The second and more important group are those associated with true forward displacement of the globe by edema and fibrosis of the retro-orbital tissues This progressive exophthalmos is essentially a self-limiting process, but the eye may be lost before the process has spent itself Above all, the cornea should be carefully protected from drying and consequent ulceration In severe cases surgical retro-orbital decompression may be indicated Dobyns recommended that the patient sleep upright to diminish the edema formation in the retrobulbar space, and that both hypothyroidism (which might result in increased pituitary secretion) and hyperthyroidism be avoided

MECHANISMS OF THE EFFECTS OF IODINE AND ANTITHYROID DRUGS IN HYPERTHYROIDISM *Inorganic iodine* Lack of iodine, which tends to interrupt the normal output of thyroid hormone, results in an increased secretion of TSH Consequently, the cells of the thyroid are stimulated and it enlarges, though the function of the gland may not be increased

In contrast, when iodine is administered to the patient with Graves' disease the thyroid gland diminishes in size, in part the result of a reduction in its vascularity However, the height of the follicle cells also declines, and the colloid within the follicles is increased in amount The precise way in which iodine achieves these effects is uncertain, but there may be effects upon both the pituitary and the thyroid gland itself It has been postulated that (1) the thyroid is rendered less sensitive to TSH, (2) the rate of thyroid hormone synthesis is suppressed, or (3) the rate of release of thy-

roxine (and of other active compounds) is reduced None of these is definitely established as the primary factor, though, and other modalities may be found more important.

Antithyroid drugs Certain compounds, such as thiouracil, propylthiouracil, and mercaptoimidazole, have a specific effect in blocking hormone synthesis They do this by inhibiting the *peroxidase conversion* of trapped iodide to iodine for the formation of diiodotyrosine, precursor of thyroxine (Fig. 223) The daily adult therapeutic dose of propylthiouracil is approximately 300 mg. though larger amounts may be required in individual patients, and the dose of mercaptoimidazole (Tapazole) is approximately 30 to 40 mg. The use of divided doses throughout the 24-hour period produces a more sustained antithyroid effect.

THE DIAGNOSIS OF HYPERTHYROIDISM. The clinical appearance of the patient who has diffuse toxic goiter with hyperthyroidism or Graves disease, often with prominent exophthalmos is known to all students and clinicians The diagnosis of hyperthyroidism in these individuals rarely presents a problem, though it is of value to assess the relative magnitude of the thyroid overactivity initially, so that the response to treatment can be better evaluated In contrast, hyperthyroidism due to nodular goiter or to excessive doses of thyroid substance may long elude diagnosis because the clinical signs are less obvious.

Clinical evidence The diagnosis of hyperthyroidism will, of course, be suspected from the history and the physical examination which reveal intolerance to hot weather, moist skin peripheral dilatation amenorrhea and weight loss associated with an increased appetite As noted previously the circulatory effects include tachycardia increased pulse pressure increased cardiac irritability and arrhythmias which often take the form of auricular fibrillation. The tremor and other nervous and muscular findings are accompanied by increased muscle irritability hyperkinetic activity, palpitation, diarrhea, myasthenia, and late muscular atrophy in some subjects In fact, it may be difficult at times to distinguish thyrotoxic myopathy from myasthenia gravis and, indeed, the two may coexist Needless to say, the presence of a goiter should always prompt careful evaluation with regard to the possibility of thyrotoxicosis Again, well developed Graves disease is not likely to be overlooked, in contrast, the elderly lady who has a solitary hyperfunctioning adenoma of the thyroid, who has lost weight and perhaps has mild cardiac decompensation may well escape accurate diagnosis until the disease has been present for a long while and circulatory changes are far advanced It was seen above that the nodular goiter often has been present for years before thyrotoxicosis is diagnosed.

Laboratory tests Once the clinical evidence has raised the suspicion that thyrotoxicosis exists, certain laboratory tests are helpful.

The *basal metabolic rate* (BMR) remains a practical guide in the diagnosis and management of hyperthyroidism. Moreover, this measurement is available almost everywhere for highly skilled technical personnel are not required

On the other hand the BMR is no longer the most reliable gauge of the rate of thyroid activity Among its disadvantages are, first, that it may be impossible to bring the patient to the test in a basal condition, though intravenous Pentothal anesthesia can be employed to achieve this requirement for the duration of the test. Of importance Benedict[17] showed that an emotional disturbance may cause a rise in the BMR which may not subside for several days Second, a repeatedly normal BMR will rule out hyperthyroidism in all but the very exceptional case, but a persistently elevated rate *does not* necessarily mean that the patient has thyroid overactivity For example, the patient may normally have had a low BMR, which has risen to the upper limits of the "normal" level during the period of increased thyroid function Third

other conditions may be associated with an increased metabolic rate—among these being pheochromocytoma, acromegaly, leukemia, essential hypertension, certain drugs, pregnancy, infections, fever, polycythemia vera and, of course, the administration of thyroid extract. Fourth, cardiac failure, asthma, emphysema, or other types of respiratory disturbances render the BMR determination unreliable, not to mention the possibility of a perforated eardrum or a leak in the machine.

The rate of *radioiodine uptake* by the thyroid gland is now established as a most dependable measurement of thyroid activity. It employs the fact that the thyroid gland traps and organically binds the administered inorganic radioactive iodine at a rate commensurate with thyroid activity (Fig. 225). This was first demonstrated by Hertz, Roberts, and Salter[58] in 1942. They found that the normal range of uptake in man lay between 10 and 40 per cent. An uptake in excess of 50 per cent of the injected iodine was held to be specific for thyroid hyperactivity, though there was a slight overlap between the euthyroid and the hyperthyroid patients.

While the tracer study has proved somewhat less dependable in nodular than in diffuse goiter, this additional test of thyroid function has proved exceedingly valuable as a clinical and laboratory tool; furthermore, the development of the scintillation counter has made possible the use of very small tracer doses, on the order of 1 μc (microcurie). This is 1/100 the former dose.

The disadvantages of the radioiodine uptake measurement are that, aside from the moderately expensive initial technical and instrumental outlay that is needed, important precautions are required to avoid false interpretations. For example, the patient must not have recently received thiouracil-like compounds or iodine therapy. In fact, it is unreliable if the patient has received iodine in any form, and the effect of lipiodol used for bronchography may persist for months. Factitial hyperthyroidism resulting from excessive treatment with desiccated thyroid for such conditions as sterility would not be detected by the radioiodine uptake study. Finally, the uptake of radioactive iodine by goiters that are partially or wholly intrathoracic often cannot be determined accurately. The urinary excretion of radioiodine is now rarely used to evaluate thyroid uptake and activity.

The *conversion ratio* is a variant of the radioiodine uptake measurement. In a series of investigations employing radioiodine as a tracer in the study of thyroid physiology Chaikoff, Taurog, and Reinhardt[28] found that the rate of incorporation of radioactive iodine into protein by the thyroid was increased in rats and guinea pigs injected with thyrotropic hormone. These workers suggested that the rate of conversion of radioactive iodine into thyroxine might be used to measure thyroid activity. Subsequently Clark, Moe, and Adams[30] found that in man the conversion ratio ranged from 13 to 40 per cent. Those patients whose conversion ratio was 50 per cent or greater were considered to have thyroid hyperactivity, and in a study of 150 patients we[8] obtained similar results. Two advantages of importance which the conversion ratio has over the uptake study are, first, that the conversion ratio is unaffected by the intrathoracic position of all or part of the thyroid gland and, second, that one can draw the blood in the patient's room for the measurement of the conversion ratio and avoid the necessity of taking the patient to the Geiger counter. In fact, commercial tracer samples are purchasable in such form that the sample may be given orally, a blood sample then drawn 24 hours later, and this shipped to a distant city for analysis of the conversion ratio.

The *protein bound iodine level* of serum (PBI) has been shown to bear a dependable direct relationship to the degree of thyroid activity, and this fraction is now considered to represent the quantitative measurement of the iodine of thyroxine and related compounds circulating in the blood stream. A carefully performed serum PBI determination provides an accurate measurement of

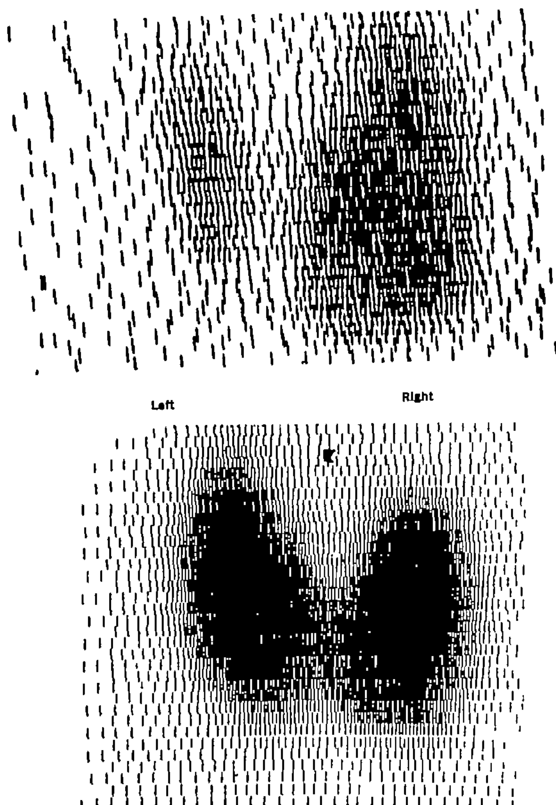


Fig 225 Scintigram performed following the administration of radioiodine The relative density of the I^{131} uptakes by different lobes reflect the relative activities of these lobes. A toxic adenoma would reflect more activity than the surrounding tissue (From Radioiodine in Medicine Spectrum 5: 165 1957)

the level of thyroid activity, provided the patient has not recently received iodine-containing compounds or thyroid extract. The injection of iodine in any form renders the test unreliable for some time and again the use of lipiodol for bronchography may cause a spurious elevation of the PBI level for as long as 15 months after the injection of the material. Nevertheless, with adequate precautions this test though laborious is su

perior to the BMR, in that it is a more objective determination and is not affected by most of the numerous conditions which render the BMR unreliable Moreover, the serum PBI level is not affected by thiouracil administration, whereas the radioiodine uptake is

The normal range of the serum PBI level lies between 3 and 8 μg (micrograms, gamma) per 100 ml of serum Values above this range indicate thyrotoxicosis and values below this range indicate a state of hypothyroidism If the serum PBI level is within normal limits, the patient almost certainly does not have thyrotoxicosis, however, this cannot be said for the BMR, since an increase in thyroid activity of 30 points (as from −15 to +15) might have taken place shortly preceding a test which showed a BMR of +15, as has been noted previously

General discussion of tests for the diagnosis of hyperthyroidism It should not be concluded that any one test of thyroid activity should be used to the exclusion of all others Each of the four tests discussed above measures a different facet of thyroid physiology and the tests supplement one another In fact, in certain situations all may be useful For example, hyperthyroidism associated with an intrathoracic goiter might not be accurately measured by the radioiodine uptake because of the goiter's anatomic location The BMR might be unreliable because of pressure upon the respiratory tract The serum protein-bound iodine level would be elevated in this instance, but the conversion ratio would be required to distinguish between factitial thyrotoxicosis and true hyperactivity of the intrathoracic goiter We reported a case in which the thyrotoxicosis was indeed factitial and was not due to hyperactivity of the patient's huge intrathoracic goiter [53]

Thyroid hyperactivity in patients who have received thiouracil compounds is best diagnosed by determination of the BMR and the serum PBI level, since even small amounts of these drugs modify the uptake of radioiodine by the thyroid for a few days If the patient has ingested iodine or iodine-containing compounds, the BMR would be the only test immediately reliable, for the serum PBI level, the conversion ratio, and the radioiodine uptake would be rendered suspect Therefore, iodine therapy should be avoided until a quantitative diagnosis of the level of thyroid activity has been made Finally, when at times a combination of circumstances has rendered all available laboratory tests unreliable, a clinical test of iodine therapy may be quite useful Knowledge of the serum cholesterol level is of no practical use in the diagnosis of hyperthyroidism

MANAGEMENT OF HYPERTHYROIDISM Hyperthyroidism may be managed conservatively or with surgery Conservative management consists of the administration of inorganic iodine, various antithyroid compounds, or radioiodine Nevertheless, only surgery and radioactive iodine administration constitute definitive therapy

It is not the purpose here to discuss in detail the merits of radioactive iodine *versus* surgery There can be little question that thyrotoxicosis due to either nodular or diffuse goiter can be controlled with radioiodine in the vast majority of instances The decision as to whether surgery or radioiodine is to be used is usually settled on the basis of whether or not radioactive iodine is available, the preference of the physician, and the preference of the patient In many hospitals where radioiodine therapy is available it is now used almost routinely, especially in Graves' disease Moreover, surgeons themselves often recommend radioiodine, particularly in the management of recurrent toxic goiter, in poor risk patients, and in patients with malignant exophthalmos In brief, the use of radioiodine has greatly reduced the number of operations performed for toxic goiter

The therapeutic objective of all forms of treatment is to reduce the amount of thyroid hormone made available to the tissues Surgery accomplishes this objective by excising

most of the functioning thyroid tissue, radioiodine by destroying thyroid cells, and propylthiouracil and iodine by suppressing hormone synthesis and release. It will be clear that a satisfactory therapeutic result may be obtained even in the absence of factual knowledge of the precise mechanism by which the thyroid is stimulated to produce excessive amounts of its hormones. External x ray has been virtually discarded as a treatment for thyrotoxicosis

Inorganic iodine is used to prepare patients for surgery and, occasionally, to treat a mild recurrence of hyperthyroidism following surgery

Antithyroid drugs The antithyroid drugs such as propylthiouracil and mercaptoimidazole are used for preoperative preparation of the thyrotoxic patient and, in some instances, as a means of definitive therapy However, the frequency of recurrence following cessation of treatment, the time and expense involved in the control of this therapy, and the distinct possibility of carcinogenesis following prolonged stimulation of the thyroid by these goitrogenic compounds have limited their use as the sole means of therapy Nevertheless, there are those who do use these agents, usually one at a time, as a definitive treatment for thyrotoxicosis. The effects of I^{131}, KI, and thiouracil on the BMR are compared in Figure 226

Thyrotoxicosis during pregnancy is often satisfactorily managed with antithyroid drugs especially during the last trimester

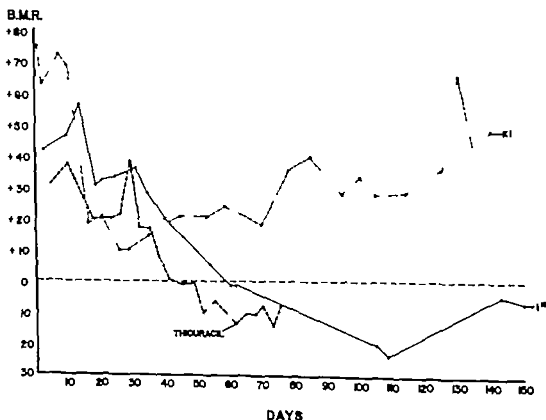


Fig 226 Potassium iodide effected a prompt, if brief remission. Thiouracil reduced the basal metabolic rate (BMR) more rapidly than did I^{131} (Potassium iodide modified from MELLANBY *Nutrition and Disease* 1934 thiouracil modified from BARR D P., AND SHORR E Ann Int. Med., **23**: 754 1945 radioactive iodine modified from KELSEY M P., HAINES S F., AND KEATING, F R. J Clin Endocrin., *9*: 171 1949)

Radioiodine is contraindicated and thyroidectomy might precipitate a premature delivery Furthermore, when the stimulus of pregnancy has subsided it will be possible to evaluate thyroid function more accurately

Actually, the effect of radioiodine is often too slow, even were this agent a safe one to use in the pregnant woman Propylthiouracil also may act too slowly, as it did in a case we observed who aborted within 48 hours after admission Some transient fetal thyroid suppression is produced by propylthiouracil therapy, but the mother must be protected from the hazards of thyrotoxicosis, in addition to the fact that she will abort if untreated

We have followed a moderate number of cases of thyrotoxicosis during pregnancy If the disease develops before the third trimester we usually recommend proper preparation followed by surgery, propylthiouracil is used for cases developing in the last trimester, as indicated

Radioiodine therapy This is an effective agent,[31] but certain limitations must be kept in mind First, it should not be administered to pregnant women, lest the thyroid of the fetus be destroyed Ovarian effects are questionable Second, there remains some question as to whether patients under 40 years of age should receive therapeutic doses of from 5 to 15 millicuries of radioactive iodine, since it is not yet certain that I^{131} will not prove to be carcinogenic in human beings (as it is in rats), from 15 to 20 years are usually required for an irradiation effect to produce cancer Third, nodular toxic goiters are not always successfully treated with radioiodine and the possibility of carcinoma residing in a solitary nodule may be overlooked (Such a patient is under care in our hospital at this writing) We believe that most toxic nodular goiters should be managed surgically

A massive dose of radioiodine may (rarely) cause a thyroid crisis (as in a case with which we were associated), and it may occasionally be advisable to bring the thyrotoxicosis under control with an antithyroid drug before the radioiodine is administered It would seem preferable to utilize graded doses of the radioiodine rather than to give a single massive dose at the beginning, no matter how accurately one thinks he can determine the size of the gland and its relative activity, as determined by the tracer study The response to radioiodine is a gradual one, and a full effect of treatment will not occur until after from 3 to 6 months Thus, the status of the patient should be reevaluated carefully before each dose of I^{131} is given One quite clear-cut indication for radioactive iodine therapy is in the management of postoperative recurrence of thyrotoxicosis, since secondary operations are particularly likely to result in recurrent laryngeal nerve injury or hypoparathyroidism

Surgical management The indications for surgical therapy, as compared with radioiodine, vary from one clinic to another and, as stated previously, no detailed examination of this changing philosophy will be offered here. In our view, the diffuse toxic goiter in most men, and in women at the end of the childbearing period, can satisfactorily and safely be managed with radioiodine—and the patient naturally prefers the drinking of a glass of water (containing the I^{131}) to operation On the other hand, we feel that at the present time most nodular goiters and some toxic diffuse goiters should be managed surgically Of course, in many areas of the United States radioactive iodine is still not readily available to patients who do not have the means to travel considerable distances, and in these individuals surgery must be relied upon

In brief, if the concern regarding possible carcinogenesis proves baseless, as it probably will, radioiodine may become the treatment of choice in most cases of thyrotoxicosis

The thyrotoxic patient may be prepared for surgery with the traditional inorganic iodine therapy, and this frequently results in an essentially euthyroid subject upon whom surgery can safely be performed However, the great advantage of propylthio-

uracil and the other antithyroid drugs is that, with these, most patients can be rendered basal and safe for surgery, whereas with iodine therapy alone there often remain individuals who will not respond satisfactorily. It is no longer permissible to perform the thyroidectomy when the basal metabolic rate has not been brought into the normal range, the pulse stabilized at a relatively slow rate, the patient improved symptomatically, and the weight loss curve reversed. The administration of antithyroid drugs in sufficient dosage for sufficient lengths of time will usually achieve this.

Both cortisone and ACTH have been used for the preoperative preparation of patients with thyrotoxicosis, but this has been done largely on an experimental basis. Since these drugs themselves often increase the rate of metabolism, they have no place except in carefully controlled experiments, in our opinion. We studied (1951) the effect of these hormones upon thyroid activity in both euthyroid and hyperthyroid subjects.[34, 35] There is no question that thyroid activity is reduced, but patients with thyrotoxicosis are better prepared for surgery with antithyroid drugs and/or inorganic iodine.

After the patient has been satisfactorily prepared for operation with one or more of the appropriate drugs and an adequate diet, a sufficiently radical thyroidectomy is performed in Graves' disease and the functioning adenoma with perhaps additional portions of the gland are resected in nodular toxic goiter. While the removal of a large portion of the thyroid gland does not influence the possible overproduction of the thyroid stimulating hormone (TSH) by the pituitary, at least not directly, it does remove much of the functioning tissue of the target organ, the thyroid. This effectively diminishes the amount of thyroxine available to the tissues to increase the rate of metabolism and in general, achieves the desired therapeutic effect.

Some patients require much more propylthiouracil for satisfactory control than do others. Since goitrogenic compounds increase the vascularity of the gland, many surgeons prefer to administer inorganic iodine in the form of potassium iodide or Lugol's solution during the week prior to operation, with or without propylthiouracil. I often do this myself, but without feeling that it is imperative.

Nutritional deficits are common in the presence of prolonged thyrotoxicosis. Fatty infiltration in the liver and protein losses should be minimized by the consumption of a high caloric, high protein diet with liberal vitamin supplements. Sedation is given for the hyperirritable neuromuscular system, and digitalization may be indicated if prolonged thyrotoxicosis has resulted in cardiac decompensation.

Physiologic Considerations in Nontoxic Goiter: Diffuse and Nodular

Simple (nontoxic diffuse) goiter is common in areas where there is an inadequate supply of iodine in the water supply. Such goiters are referred to as endemic goiters and may be experimentally produced in animals by placing these animals on iodine-deficient diets. They can also be produced by giving goitrogens which interfere with thyroxine synthesis by the thyroid. A good descriptive term is that of "iodine-deficiency thyroid hyperplasia." The enlargement of the thyroid occurs because the thyroxine formation is depressed due to an inadequate supply of iodine or to the effect of goitrogens. The diminished plasma level of thyroxine results in an increased function by the anterior pituitary in secreting TSH and thyroid hyperplasia results; this is associated with an increase in the weight of the thyroid, a decrease in the amount of colloid in the follicles, and an hyperplastic increase in the height of the lining epithelial cells. The iodine content of such a thyroid is, of course, quite low, and there is an extremely low concentration of thyroxine in the gland. The follicles may contain much colloid, but the colloid contains little thyroxine.

The *treatment of colloid goiter* should be considered from both the prophylactic and

the therapeutic standpoints Prophylactically, the addition of small amounts of iodine to table salt or to drinking water all but eliminates the formation of endemic goiter Once the goiter has formed, medical therapy may or may not be effective in causing it to regress While iodine therapy has been recognized as effective in endemic goiter, it is generally realized that it is of little value in sporadic goiter Nevertheless, most simple goiters should be treated first with iodine therapy to see if this will help Should the nontoxic goiter not regress under simple iodine therapy, thyroid hormone may be used Greer and Astwood[50] reviewed the reported experience with the treatment of nontoxic goiters with thyroid substance, and added 50 cases of their own treated over a 5-year period Seventy-six per cent of the patients responded to therapy with a decrease in the size of the goiter and 40 per cent had a complete remission Only 2 relapses were observed during the 1 to 7 years of observation following treatment Eighty-seven per cent of 23 diffuse goiters responded to therapy, 44 per cent undergoing complete remission Sixty-seven per cent of 9 multinodular goiters had a favorable response, 23 per cent disappearing completely Sixty-seven per cent of 18 single nodules responded and 39 per cent disappeared completely. Only 15 per cent of 40 goitrous patients not treated with thyroid had a reduction in the size of the goiter These workers stated that iodine may be effective when iodine deficiency is the major etiologic factor, or when the primary defect is a failure of the iodine-concentrating mechanism of the thyroid If, however, the defect lies beyond the stage of iodine concentration, such therapy may well fail Thyroid substance, on the other hand, will decrease the secretion of thyrotropin and, in turn, the size of the goiter, regardless of the nature of the defect in hormone synthesis, in this sense, then, desiccated thyroid might be regarded as a specific in the treatment of goiter Greer and Astwood further noted that, as a practical therapeutic measure, the administration of thyroid has certain advantages In addition to its beneficial effect upon the size of the goiter in 3 out of 4 cases, thyroid administration aids in the diagnosis in doubtful cases Failure of the goiter to respond and failure of the radioiodine accumulation to be suppressed constitutes suggestive evidence for a diagnosis of hyperthyroidism They acknowledged that the significance of single thyroid nodules is currently controversial Some feel that all such nodules should be removed because from 10 to 20 per cent of them are considered malignant (Fig 227) at pathologic examination, others feel that the death rate from carcinoma of the thyroid is so low that the likelihood of death from thyroid surgery is greater than the likelihood of saving a life by the routine removal of solitary thyroid nodules

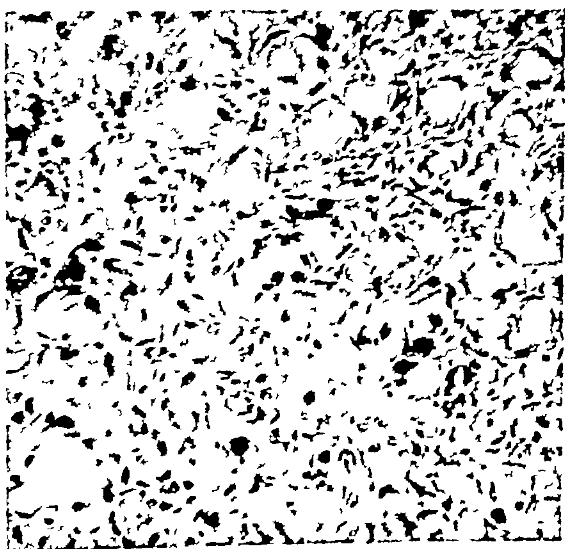


Fig 227 Carcinoma of the thyroid in center of solitary nodule This lesion, barely large enough to fill the low power field under the microscope, was found almost by accident

The finding that solitary nodules often respond to thyroid indicates that their hyperplastic state is of a physiologic and not a neoplastic nature, in the view of Greer and Astwood For example, simple enlargement of the thyroid gland is generally accepted as functional hypertrophy, even though the other lobe is completely normal in size It is usually assumed that one lobe is more sensitive to thyrotropin than the other In any event, thyroid therapy seems to be as

beneficial in unilateral thyroid enlargement as in bilateral enlargement. It is possible that a single nodule represents a localized area which has a lower thyrotropin threshold than the rest of the gland, since the response of the nodules noted in Greer and Astwood's[50] series was not greatly different from that of other types of goiter They administered from 2 to 3 grains of desiccated thyroid daily, the extremes ranging from ½ to 6 grains.

It should be stated, however, that not all diffuse or nodular nontoxic goiters respond to iodine therapy We favor excision of the goiter which appears to have a single hard nodule—and we are well aware that other nodules may exist which are not palpable preoperatively The simple colloid or nontoxic goiter may also require surgery because of compression of the trachea and other neighboring structures, and for cosmetic reasons. In Figure 227 is shown a microscopic section from a soft nodule removed from the neck of a lawyer It was considered almost surely benign, but he was anxious that it be removed. The mass about 2 cm in diameter, constituted most of the right thyroid lobe. In the center the pathologist found, almost accidentally, this virtually microscopic carcinoma.

Post Thyroidectomy Complications

INJURY TO RECURRENT LARYNGEAL NERVES Routine preoperative visualization of the vocal cords should be performed to ascertain that both laryngeal nerves are intact. If one cord is found not to move satisfactorily preoperatively then one must be doubly careful in dissecting on the opposite side to avoid the possibility of injury to the other recurrent laryngeal nerve Except for the hoarseness (which improves with time) actual division of one nerve is usually not accompanied by serious consequences. However injury to both nerves will frequently require a permanent tracheostomy for respiratory obstruction. Various operations have been devised to remedy the situation caused by injury to both recurrent laryngeal nerves, but these procedures are not particularly satisfactory

More frequently the nerve has merely been traumatized, not cut, and one may expect complete recovery with considerable confidence If both cords move well immediately postoperatively—and to look takes but a moment—the development of hoarseness at the end of from 24 to 48 hours is almost certainly the result of an inflammatory edema that will subside

The incidence of recurrent laryngeal nerve injury should be less than 1 per cent, but it is probably more nearly 3 to 4 per cent If one is doing a radical operation for a cancer of the thyroid it is at times impossible not to take the nerve on one side, since it may be completely surrounded by the tumor

HYPOPARATHYROIDISM. Just as the nerves should be visualized when a radical subtotal resection is contemplated so also should the parathyroid glands be visualized when the posterior thyroid capsule is to be removed, as in total thyroidectomy It follows, then, that the surgical resident must become familiar with the appearance and approximate location of both the nerves and the parathyroids At least one parathyroid should be identified and left *in situ*, if hypoparathyroid tetany is to be avoided consistently If a parathyroid is inadvertently separated from its blood supply one can implant it in the adjacent sternocleidomastoid muscle. A number of small fat lobules or lymph nodes may have some resemblance to the parathyroid but this gland is usually identifiable when actually visualized If doubt remains, a small portion can be submitted for frozen section

If the parathyroids have all been removed —or if only three have been removed but the blood supply to the remaining one is temporarily diminished—the signs and symptoms of hypoparathyroidism will appear by the end of 24 hours and not later than 48 hours as a rule. The most common of these is a tendency to carpopedal spasm and tingling of the feet, legs, and hands

Confirmatory evidence is gained by demonstrating a positive Chvostek's sign, which consists of lightly tapping the facial nerve in front of the ear and noting the spasmodic contractions of the muscles of the face and particularly those around the mouth In addition, if carpal spasm is not already present the inflation of a blood pressure cuff on the upper arm will usually produce it (Trousseau's sign) Such findings following thyroidectomy should always suggest the possibility of hypoparathyroidism with hypocalcemic tetany The management of this condition may be carried out in the following steps

(1) First draw blood for serum calcium and phosphorus determinations, before therapy has masked the chemical picture

(2) Give 10 to 20 cc of 10 per cent calcium gluconate solution intravenously at once

(3) Give calcium gluconate or calcium lactate (lactate is better absorbed than gluconate) by mouth Approximately 12 gm per day in divided doses will usually suffice

(4) Give vitamin D orally in doses of from 50,000 to 300,000 units daily

(5) If vitamin D and calcium lactate, plus supplements of intravenous calcium gluconate, fail to control the tetany, parathormone should be given parenterally in doses of 100 units, as necessary to relieve symptoms The effect of this hormone is short lived, and the dose may need to be repeated a number of times before the oral vitamin D therapy has had effect

(6) If the increased calcium made available by vitamin D therapy should prove inadequate, dihydrotachysterol (A T 10) may be administered for maintenance therapy in oral doses of from 5 to 10 cc daily initially, followed by 2 cc twice weekly However, this substance has a definite cumulative action, and its administration must be controlled by frequent serum calcium determinations

Dihydrotachysterol should not be started until it has been amply demonstrated that the hypoparathyroidism is to persist for some time Many surgeons make the mistake of giving A T 10, a long acting drug, when oral calcium therapy would have sufficed If dihydrotachysterol is not administered, one will usually be relieved to find, within a few days, that the hypoparathyroidism is temporary and that the patient may safely go home without any calcium or other therapy On the other hand, if A T 10 has been given, the operator may have to wait 6 or 8 weeks to be certain of the status of parathyroid function, and this is never as happy a situation as had the patient been discharged with the diagnosis of hypoparathyroidism reversed or changed to "transient"

POSTOPERATIVE HEMORRHAGE WITH RESPIRATORY OBSTRUCTION The most sinister single complication following thyroidectomy is that of hemorrhage leading to respiratory difficulty and, all too often, to death This is particularly likely to be disastrous in that it often occurs when the patient is no longer in the operating room or the recovery room, and close observation may have been discontinued The complications of recurrent laryngeal nerve injury and parathyroid tetany do not usually occasion immediate disaster, though they must be handled expeditiously On the other hand, respiratory obstruction due to hemorrhage may not be recognized until the situation is all but irretrievable The onset is usually insidious and may go unnoted or, if noted, then unappreciated for a time At first there may be not more than a subjective feeling of tightness in the neck and an objective appearance of fullness Presently the patient becomes dyspneic, and this may be the last warning before a most alarming state of respiratory distress and cyanosis suddenly intervenes The chief difficulty lies in the fact that the hemorrhage is deep to the fascia and no bleeding may be noted externally Moreover, while adequate drainage at the time of closure may diminish the incidence of obstruction due to hemorrhage, concealed bleeding may still occur *A tracheotomy set should be kept on all floors* Furthermore,

the wound should be re-explored and tracheostomy seriously considered at the first evidence of respiratory obstruction. The resident staff must be thoroughly indoctrinated with the concept that the time to do a tracheostomy is when one is first forced to think of it. Fortunately, the general tendency to perform tracheostomy earlier in a variety of clinical circumstances has diminished the incidence of fatal postoperative respiratory obstruction due to hemorrhage.

THYROID CRISIS This is now a most infrequent complication of thyroid surgery or thyroid disease but it does occur, and we have observed two cases in the past few years, both in children. In one instance the mother had refused to bring the child back for treatment of known hyperthyroidism until finally the child was admitted in thyroid crisis and died within a few hours despite hydrocortisone and other therapy The second youngster was under treatment for several months and the case brings out certain important points

Case study The patient was a 6-year-old girl who exhibited evidence of weight loss mild exophthalmos and a rapid pulse when the mother first brought her to the hospital for examination. The clinical examination suggested hyperthyroidism since a goiter was also present and excessive thyroid activity was proved by (1) the uptake of radioactive iodine (2) determination of the serum PBI level (which was elevated) and (3) several somewhat unsatisfactory measurements of the basal metabolic rate Following this over a period of many weeks the child was given several of the antithyroid drugs (particularly propylthiouracil) in adult dosage (600 mg. per day) after early failure to obtain a satisfactory response with lesser amounts. Suffice it to say that none of the antithyroid drugs achieved a basal condition The radioiodine committee met—internist, radiologist, and surgeon—and after a careful review of the case decided *against the use of radioiodine*. It was elected to give inorganic iodine for 10 days and then to do a subtotal thyroidectomy she remained sweaty and tremulous cardiac failure appeared imminent even with digitalis therapy, and she had gained no weight. Here, then, was a patient who had not *responded satisfactorily to treatment* with large dosages of antithyroid drugs.

She was placed on iodine therapy and, though she improved somewhat, she did not become truly basal. Nevertheless, at a general staff conference it was decided that she was probably safe for thyroidectomy and that it should be performed at once. Accordingly, subtotal thyroidectomy was expeditiously performed after 10 days of iodine therapy The pulse rate rose from the preoperative level of 88 to 110 beats per minute during the operative procedure, and at the end of operation it had reached a rate of approximately 140 beats per minute. Approximately 2 hours following operation the rectal temperature had risen to 105° and the pulse rate had increased to approximately 200 per minute. The respiratory rate had climbed alarmingly, and her general condition appeared critical. Since the possibility of crisis had been anticipated, sodium iodide hydrocortisone, and ACTH were on hand and were promptly started intravenously An oxygen tent and water-alcohol sponging were used to combat the hyperthermia. Unfortunately, despite all measures the temperature rose to 106 by rectum and the pulse rate became so rapid as to defy accurate count. The respiratory rate had become extremely fast, and presently the child developed pulmonary edema with copious pink frothy sputum. All supportive measures were unavailing, and she died *approximately 5 hours after the operative procedure* in what was interpreted by all observers as thyroid crisis She had not received excessive transfusion of blood during operation and little blood had been lost.

Comment This case illustrates a number of pertinent physiologic facts In retrospect, since a truly basal state was never achieved preoperatively the possible dangers of radioactive iodine in a young person should have been accepted and the agent used. In other words, surgery should no longer be employed in a patient who cannot be rendered

basal Second, in our experience no satisfactory therapy exists for the patient who is in severe thyroid crisis Surgery was undertaken in this girl partly because of reports in the literature which had led us to believe that, should thyroid crisis develop, it could be controlled reasonably well with adrenocortical replacement therapy Such was not the case The patient received massive doses of these compounds immediately following operation and they had no visible effect on the thyroid crisis, as they had no effect in the other child who was admitted in thyroid crisis and died It may well be that the patient who has relatively mild thyroid storm will respond satisfactorily to treatment with adrenocortical replacement therapy, for adrenal steroid therapy can reduce thyroid activity Nevertheless, be this as it may, the best possible treatment for thyroid crisis is to avoid it, for effective therapy for the full-blown case has yet to be developed.

MALIGNANT EXOPHTHALMOS This condition has been discussed previously and is not strictly a complication of thyroidectomy Yet, the exophthalmos often does increase following thyroidectomy, and some have actually treated this complication with desiccated thyroid in fairly liberal doses The rationale for this is that the exogenous thyroid hormone may suppress pituitary activity, which is presumed to be the source of the stimulus for the exophthalmos Moreover, certainly hypothyroidism, with its deposits of edema fluid and possible stimulation of pituitary acitivity, is to be avoided Notwithstanding, no genuinely suppressive therapy is available

A marked exophthalmos which appears to be progressing is considered by many, including myself, to be an indication for radioactive iodine rather than surgery There has been evidence that thyroidectomy increases the rate of progression of the exophthalmos in some subjects, and it has been considered possible that the more gradual reduction of thyroid activity with I^{131} therapy is preferable to thyroidectomy

RECURRENT THYROTOXICOSIS The recurrence rate following subtotal thyroidectomy varies with the amount of gland removed at operation and should be in the neighborhood of 5 per cent or less if from four-fifths to five-sixths of the gland are removed at the time of surgery Obviously, the lower the recurrence rate, the higher will be the incidence of hypothyroidism postoperatively, and one must use judgment in the individual case A more radical resection, with a greater risk of hypothyroidism, is more permissible in older persons who have matured than in younger individuals who will need normal thyroid activity to achieve the normal development of other organs Postoperative recurrence of hyperthyroidism may require nothing more than inorganic iodine dosage or perhaps a course of propylthiouracil If these simple measures do not suffice, radioiodine is effective

Postoperative hypothyroidism is treated with appropriate doses of thyroid substance

Relation of Thyroid Gland to Other Endocrine Glands

As has been emphasized throughout this volume, all organs are interdependent and the thyroid gland is no exception It has been seen that a close relationship exists between the thyroid and the pituitary, since the removal of the pituitary is followed by involution of the thyroid and a state bordering on myxedema is produced On the other hand, total thyroidectomy may result in pituitary hypertrophy in some animals

Another most interesting relationship is that which the thyroid and the adrenal cortex appear to bear to each other It is well known that the administration of adrenocortical substance results in a rapid lysis of lymphoid tissue and that lymphoid tissue is increased in hyperthyroidism Furthermore, the administration of adrenocortical substance was shown to diminish thyroid activity It was further shown by White and Dougherty[105] that the administration of adrenocortical extract results in the mobilization of nitrogen in lymphoid

tissue and that the administration of thyroxine increases mobilization of nitrogen from the muscles, each will result in the mobilization of some nitrogen from the liver but both together effect a greater mobilization than the sum of that mobilized by either hormone alone The appearance of the patient in thyroid crisis suggests certain of the features of adrenocortical crisis, and various workers have reported beneficial results with the use of adrenocortical substances in hyperthyroidism While adrenocortical hormones may not save the patient in severe thyroid crisis, there is no doubt that the administration of cortical hormones tends to suppress thyroid activity

The thyroid often enlarges at puberty during menstruation and pregnancy, and may change at the menopause Normal development of the gonads is dependent upon normal thyroid activity Fertility is reduced in hypothyroidism and thyroid therapy often improves the reproductive function in such individuals. For example, sterility and habitual abortion may be favorably influenced by the administration of thyroid extract. Corresponding changes may be seen in the male reproductive function particularly with regard to spermatogenesis.

Thyroiditis

Inflammation of the thyroid may be due to demonstrable bacterial agents (brucellosis in one case we saw) or, far more commonly to idiopathic or chemical" derangement in which no specific etiologic factor can be identified. Accordingly, as is so often true when the cause of a disease is obscure the treatment is largely empiric, though frequently effective

SUBACUTE THYROIDITIS This disease of unknown etiology affects women twice as often as men and occurs chiefly between the ages of 20 and 50 The involved portion of the gland, one lobe or the entire organ, usually exhibits swelling and tenderness. The tissue is firm and the overlying skin may be reddened Systemic reaction is usually not a prominent feature but fever and chills may develop The condition usually runs a self limiting course over a period of weeks or months

Among the *treatments* that have been beneficial in individual cases are roentgen therapy antithyroid drugs (specifically propylthiouracil) cortisone and occasionally, desiccated thyroid. Antibiotics are usually not helpful. When the involved portion of the gland is resected surgically it reveals evidence of a diffuse inflammatory process, and leukocytic infiltration and giant cells are seen

CHRONIC THYROIDITIS *Riedel's struma ('Woody thyroiditis')* This is a chronic inflammatory fibrosing condition which may involve only one lobe or both lobes. It presents as a hard "goiter" which may be somewhat tender, but the principal problem is *to distinguish this lesion of unknown cause* from cancer Even at operation, the involvement of contiguous tissues in the inflammatory process may render it most difficult to exclude thyroid malignancy

Treatment consists of excising enough of the inflammatory mass to relieve pressure symptoms. Radical resection involves considerable risk of nerve injury and hypoparathyroidism The various medical measures given above for acute and subacute thyroiditis are generally ineffective in the management of Riedel's struma.

Hashimoto's struma (*struma lymphomatosa*) This is a chronic degenerative disease of the thyroid, characterized by marked lymphocytic infiltration, and it appears chiefly in women of middle age The thyroid *enlargement is firm but essentially* nontender Here too, the cause is unknown. Some consider the condition a form of chronic thyroiditis, but others believe it represents the effects of primary hypothyroidism the pituitary stimulus is increased in the absence of sufficient thyroid hormone, and thyroid enlargement occurs.

Roentgen therapy may retard the disease, after confirmation of the diagnosis by biopsy but excision may be required to relieve pressure effects

The Parathyroid Glands

The management of hypoparathyroidism following thyroidectomy was discussed above Normal parathyroid physiology and hyperparathyroidism will now be considered

Historical Notes

In 1891 Gley[48] showed that removal of the parathyroid glands led to tetany, explaining the findings that had been observed following thyroidectomy In 1908 MacCallum and Voegtlin[72] found that the tetany was due to a lowering of the blood calcium level Collip[32, 33] discovered parathormone in 1925

Meanwhile, von Recklinghausen[91] had described the cystic changes in bone in 1891, Askanazy (1904)[4] had found a parathyroid tumor at autopsy in a case of the disease, and Erdheim[43] had shown that the parathyroid glands were enlarged in rickets, osteomalacia, and pregnancy. Thus the groundwork had been laid for the demonstration that parathyroid overactivity could produce disease of bones In 1925 Mandl,[75] a Viennese surgeon, excised an adenoma and demonstrated recalcification of the demineralized bones

In subsequent years the classic metabolic studies of Aub, Albright, Cope, and others of the group at Harvard greatly extended the parameters of our own knowledge of parathyroid disease

Normal Physiology

REGULATION OF PARATHORMONE SECRETION The factors which regulate the formation and release of parathormone by the parathyroids are rather more obscure than in the case of the thyroid and adrenal secretions To begin with, no tropic hormone from the pituitary has been demonstrated for these glands, and thus regulatory mechanisms have had to be sought within the glands themselves Carnes, Pappenheimer, and Stoerk[21] found that rats fed a diet low in calcium developed marked enlargement of the parathyroid glands, a diet high in calcium but low in phosphorus resulted in a significant reduction in parathyroid volume, in comparison with that of the stock diet controls The addition of gradual increments of potassium phosphate to the low phosphorus, high calcium diet increased the serum phosphate level proportionately and caused a corresponding increase in parathyroid volume These workers also found that large doses of viosterol further reduced the size of the parathyroids on a low phosphorus diet, at the same time raising the serum levels of both calcium and phosphorus Viosterol inhibited the hyperplasia produced by a low calcium diet Patt, Wallerstein, and Luckhardt[89] also showed that parathyroid hypertrophy could be produced by a low calcium diet These authors demonstrated that the perfusion of the isolated thyroparathyroid apparatus of the dog with decalcified blood resulted in a perfusate which caused a rise in the serum calcium level when injected into normal dogs This did not result when the infusion was done with normal blood Therefore, it would appear that the serum calcium level is important in regulating the rate of parathormone formation in man The liberation of this principle appears to be independent of nervous control and, as noted, counterbalancing forces from other endocrine organs have not been described

ACTIONS OF PARATHORMONE The primary function of the parathyroid hormone (or hormones?) is to regulate the blood levels of inorganic calcium and phosphorus, largely by controlling renal excretion of these ions The injection of parathormone increases the rate of phosphorus excretion (Fig 228) This is followed by a mobilization of phosphorus from the bones in an attempt to maintain a normal level of serum phosphorus, which in turn results in the mobilization of calcium (Fig 229) The increased amount of calcium phosphate thus made available raises the serum calcium level It is thought by some that the mere lowering of the serum phosphorus level by increasing phosphorus excretion in the urine (with parathormone) results automatically

a reciprocal rise in calcium, since these two elements almost invariably bear a reciprocal relationship to each other in physiologic states.

The studies of Tweedy, Chilcote and Patras[109] with radioactive phosphorus supported the earlier view of Aub that the parathyroid glands have their primary influence on phosphorus metabolism through a direct action on the kidney tubules to increase the excretion of phosphorus. They found that following thyroparathyroidectomy the early diminution in urinary and fecal excretion of administered phosphate tagged with P^{32} could be reversed within 1 hour by the injection of parathyroid extract. After bilateral nephrectomy this material had no effect on the distribution, retention, or excretion of P^{32}.

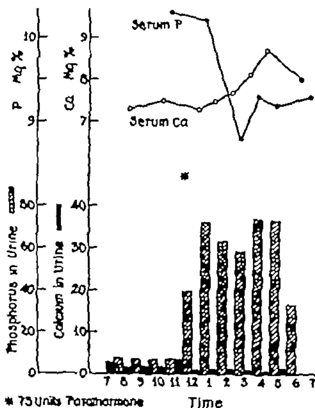


Fig. 228. Effect of parathormone on calcium and phosphorus metabolism in a case of idiopathic hypoparathyroidism. (From Albright, F. and Ellsworth, R. Studies on the physiology of the parathyroid glands. I. Calcium and phosphorus studies on a case of idiopathic hypoparathyroidism. J. Clin. Invest. 7: 104, 1929.) Note that almost immediately following the injection of 75 units of parathormone the urine phosphorus content rose, the serum phosphorus level fell, and the serum calcium level rose.

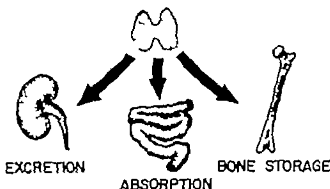


Fig. 229. Calcium metabolism embraces bone storage, renal excretion and intestinal absorption. Parathormone regulates the serum calcium level largely through its promotion of phosphorus excretion (Fig. 228). However, in post-thyroidectomy hypoparathyroidism the action of injected parathormone is so short-lived as to render it unsuitable for long term maintenance. Liberal doses of calcium lactate (12 gm. per day) and vitamin D (orally) may suffice; if not, A.T. 10 must be used.

All agree that the primary effect of parathormone is on the renal excretion of phosphorus.[6] Nevertheless a direct effect on the bones themselves cannot be entirely excluded on the basis of the evidence at hand. Some cancers alter calcium metabolism.[7, 80]

Normally the calcium and phosphorus levels of serum remain fairly constant. When excessive amounts of parathyroid tissue are removed at thyroidectomy, the serum calcium level declines and the phosphorus level rises. For example, the calcium level (normal 10 mg. per 100 cc. or 5 mEq. per L.) may decline to 6 mg., the serum phosphorus level (normal 4 mg. per 100 ml.) may rise to 6 or 7 mg. The opposite effects are observed in hyperparathyroidism.

Hyperparathyroidism: Diagnosis and Management

Hyperparathyroidism may be *primary* or *secondary*. The primary type is that which is due to primary disease within the



Fig 230 Renal calculi secondary to functioning parathyroid adenoma (Patient B L, see text)

parathyroid glands themselves, usually a functioning adenoma but occasionally the result of diffuse hyperplasia[92] Secondary hyperparathyroidism is associated with diffuse hyperplasia of the parathyroid glands, secondary to impaired renal function A commonly accepted theory is that in patients with chronic renal failure phosphate is not excreted in normal amounts and its concentration in body fluids rises The rise in phosphate ion concentration depresses the calcium ion to below normal levels (Ca × P = K, or constant), and this in turn calls forth a compensatory overactivity of the parathyroids in an effort to maintain a normal calcium level This cellular hyperplasia has been well documented in chronic renal insufficiency by Pappenheimer and Wilens[88] and by Castleman and Mallory[25, 26] An associated demineralization of bones in childhood is sometimes referred to as "renal rickets" In the presence of extensive renal damage it may be difficult, if not impossible, to distinguish between primary and secondary hyperparathyroidism, for chronic primary hyperparathyroidism also usually causes death through renal failure

The lesions found in states of *primary hyperparathyroidism* are chiefly in the parathyroids, skeleton, and kidneys The excessive parathormone production is almost invariably due to a functioning parathyroid tumor which may lie either in the neck or in the mediastinum More than one tumor may be present, but usually only one parathyroid is enlarged The excessive hormonal activity results in demineralization of the skeleton with cyst formation, pathologic fractures, and other changes associated with osteitis fibrosa cystica (von Recklinghausen's disease of bone) In approximately 30 per cent of cases of primary hyperparathyroidism the excessive hypercalcemia results in the formation of renal stones, and the renal damage secondary to nephrolithiasis often produces uremia if the process is not reversed by excision of the tumor *It has been estimated that perhaps 10 per cent of all patients with renal stones have hyperparathyroidism* (Fig 230)

DIAGNOSIS The diagnosis of primary hyperparathyroidism begins with the suspicion that it exists When renal stones or bone demineralization is found, *serum calcium, phosphorus,* and *phosphatase levels* should be determined in all patients who have renal stones or who have pathologic fractures that cannot be explained on some other basis such as metastatic carcinoma However, "metastatic carcinoma" may reflect parathyroid adenoma (patient E H, p 562)

There are definite *symptoms* that accompany the elevated calcium level which occurs in hyperparathyroidism Among these are muscular atony, weakness, fatigue, constipation, anorexia, weight loss, nausea, polyuria, and polydipsia Nevertheless, these phenomena are not sufficiently distinctive, of themselves, to suggest parathyroid adenoma The renal complications are the result of a deposition of calcium in the kidneys The calculi may cause pain, infection or, eventually, uremia

Important diagnostic points are given in Figure 231 The ultimate diagnosis rests upon the laboratory demonstration of *hypercalcemia, hypophosphatemia,* and *hypercalciuria* For the diagnosis of hyperparathyroidism the serum calcium level should be greater than 12 or 12 5 mg per 100 ml of serum However, it is important to realize

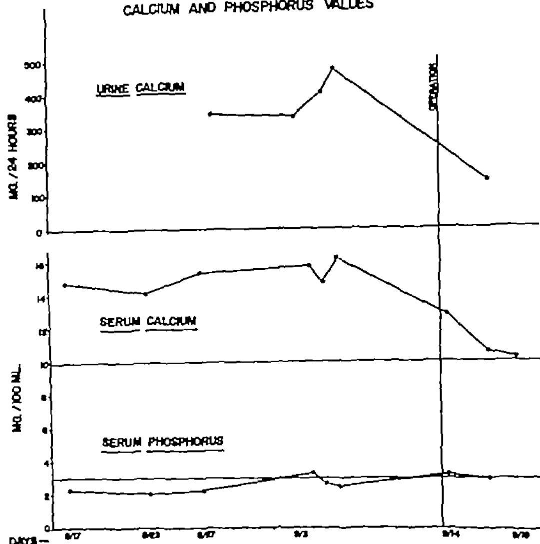


Fig 231 This patient (B L) had renal stones that led to investigation for hyperparathyroidism The urinary calcium excretion on a low calcium diet (in essence a diet free of milk and milk products) was consistently above 300 mg. preoperatively but the level fell after removal of the tumor The normal subject excretes less than 300 mg. of calcium per 24 hours on a low calcium diet The serum calcium consistently exceeded the upper limit of normal (12 mg per 100 cc) before operation but declined thereafter As was to be expected, the serum phosphorus level was somewhat depressed on several occasions preoperatively Note the prompt decline in urine and serum calcium values following resection of the parathyroid adenoma shown in Figure 232 The serum phosphorus level rose The renal stones were removed surgically Renal failure due to chronic infection around calculi is the most common cause of death in hyperparathyroidism (From NELLY W A AND ALVIS J L. Functioning parathyroid adenomas. The Mississippi Doctor 35: 68 1957)

that the level may not be consistently elevated and that several determinations should be made at different times, often several weeks apart, to rule in or rule out an elevated serum calcium level. In 12 of 24 cases Keating[64] found that the *average* concentration of calcium was less than 12.5 mg. per 100 ml of serum. In 4 cases the average level fell within the normal range and in 7 cases one or more *determinations* fell within the normal range Again calcium determinations over a period of weeks or months may be *necessary to detect the* hypercalcemia of hyperparathyroidism.

A definitely lowered serum inorganic *phosphorus level may be of particular aid* in those patients in whom the serum calcium level is within normal limits or only

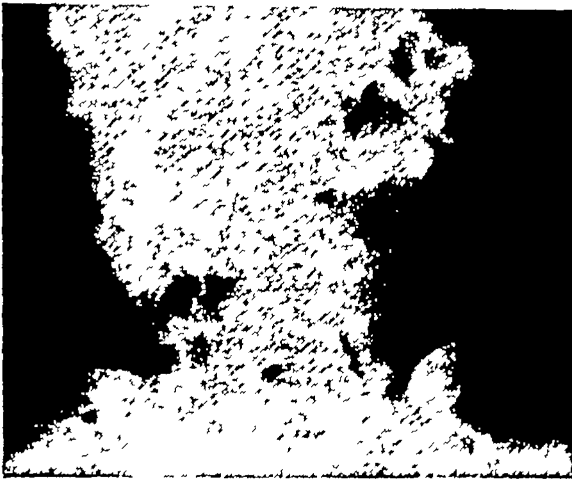


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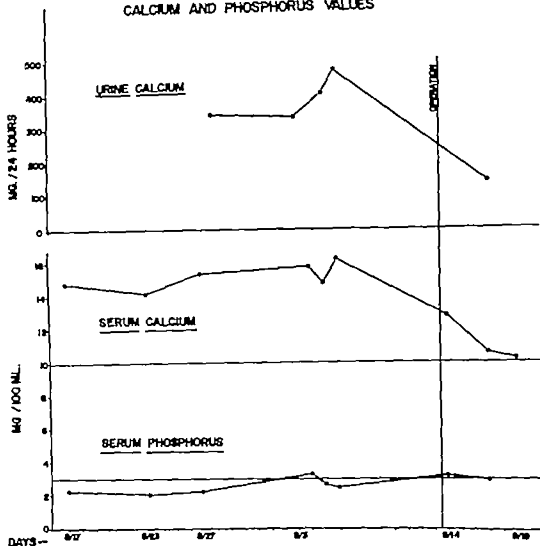


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A definitely lowered serum inorganic phosphorus level may be of particular aid in those patients in whom the serum calcium level is within normal limits or only

slightly elevated In addition, the serum *alkaline phosphatase level* is often elevated in hyperparathyroidism This is probably due to the bone disease and not to the hyperparathyroidism *per se*, the serum phosphatase level may remain elevated long after the serum calcium and phosphorus levels and the urinary excretion of calcium have returned to normal

Measurement of the *urinary calcium excretion* is most helpful in reaching a diagnosis of hyperparathyroidism If the urinary calcium excretion is elevated, hyperparathyroidism must be considered, even if the serum calcium level is normal On a low calcium diet (in essence, no milk or milk products) the normal 24-hour excretion should be less than 300 mg, and values above this figure indicate hyperparathyroidism unless otherwise explained Barney and Sulkowitch[12] proposed a screening test which is useful The patient is placed on a low calcium diet for 3 days, and then the urine is collected for 24 hours A buffered oxalate mixture is added to an aliquot of the specimen If more than a trace of calcium precipitate occurs on mixing with the buffer solution, hyperparathyroidism is suggested If indicated, the more exacting balance study of Bauer and Aub[14] can then be performed Howard[60] has proposed an intravenous calcium tolerance test for the detection of hyperparathyroidism, but we have had no experience with it

Note on calcium fractions The total serum calcium concentration is dependent upon the serum protein concentration, and for this reason the levels of both must be determined The calcium bound to protein varies with alterations in the serum protein level, and it is not primarily affected by parathormone In contrast, ionic calcium is specifically affected Thus, the individual with a lowered serum protein level but a normal total serum calcium level may still have an increased (but masked) ionic calcium level, caused by hyperparathyroidism Although the free (ionic) and the bound calcium levels cannot be determined individually, their relative concentrations can be estimated by the use of the nomogram prepared by McLean and Hastings[78] For example, the hypercalcemia of multiple myeloma or sarcoidosis would be found to be paralleled by a rise in serum protein, indicating that the increased calcium level was due to the increased serum protein level The theoretical possibility that a lowered serum protein level can mask hyperparathyroidism is rarely encountered in practice

Physical examination Unless the individual has lost stature or had other bony deformities, little may be found on clinical examination The parathyroid adenoma is usually not palpable but occasionally it is

Pancreatitis in hyperparathyroidism Instances of pancreatitis have been reported in association with hyperparathyroidism, and such a case will be described below Moyer[84] believes that deranged calcium metabolism may play a basic rôle in the pathogenesis of ordinary pancreatitis

Peptic ulceration in hyperparathyroidism Just as the "ulcerogenic" tumor of the pancreas has been shown to give rise to a particularly vicious type of peptic ulceration, so may parathyroid tumors promote this disease, the ulcer may heal promptly when the tumor is removed[36] Adrenocortical and adrenal medullary tumors may also produce peptic ulcer

Differential diagnosis Other conditions that cause bone lesions must be excluded Some of these are adolescent rickets, osteomalacia associated with idiopathic steatorrhea, senile osteoporosis, carcinosis of the skeleton (see patient E H, p 562), multiple myeloma, Paget's disease, fibrous dysplasia of bone, and the bone lesions of sarcoidosis. Renal stones may follow a variety of known and unknown pathologic circumstances

OPERATIVE MANAGEMENT OF HYPERPARATHYROIDISM The treatment of hyperparathyroidism usually consists of surgical excision of the adenoma Much less frequently the parathyroids may exhibit generalized hyperplasia such as is encountered in diffuse goiter or in adrenocortical hyperplasia

Parathyroid adenoma In 1931 Walton[102] reported operations upon 4 patients with hyperparathyroidism due to adenomas of the parathyroid glands and he was the first to call attention to the importance of searching for abnormal parathyroid tissue in regions other than about the thyroid gland. In 2 of his patients parathyroid glands had been mechanically displaced from their original positions, and he noted that in such displacements the original vascular pedicle connecting the tumor to the thyroid artery had been preserved. In 1936 Churchill and Cope[29] clearly correlated the various locations in which adenomas were found with the embryogenesis of the parathyroid glands. Churchill further postulated that the parathyroid glands would probably be found within the limits of the tubular fascial structure of the neck, bounded anteriorly by the deep layer of the middle cervical fascia and posteriorly by the prevertebral fascia. Following these reports surgeons were led to perform a systematic surgical dissection of the cervical region as well as of the posterior superior and anterior mediastinum.

The *operative exposure* for exploration of the neck and mediastinum for parathyroid adenoma should be meticulous and an adequate search for parathyroid adenoma requires a knowledge of the appearance of the normal parathyroids In our experience the tumor has more often been found near one or the other of the inferior poles of the thyroid However, the upper parathyroid glands are more constant in position and are exposed first. If they are found and are normal they are not removed. Atrophy of the parathyroids that are found suggests the presence elsewhere of an hyperfunctioning adenoma If the upper parathyroids are found to be normal or somewhat atrophied the lower ones are searched for in the same careful manner though it is to be remembered that they may not be found in the neck but that one or more may be found in the superior mediastinum If an adenoma has not been found and all parathyroids are not found in the neck, the sternum is then split and the anterior and posterior mediastinum explored. The thymus particularly should be carefully examined, for it may contain the adenoma. One or more parathyroids may lie within the capsule of the thyroid gland itself To repeat the normal parathyroids should not be removed as they are exposed, for subsequent excision of the adenoma may then render the patient hypoparathyroid for life a very serious complication

There may be more than one adenoma, but this is decidedly unusual Moreover, approximately 80 per cent of adenomas are found in the cervical region or in the posterior superior mediastinum It is the adenomas located in the anterior mediastinum that are most commonly missed. Malignancy may develop in an adenoma [37]

Parathyroid hyperplasia (primary) In 1947 Black and Sprague[21] reported the first case of diffuse parathyroid hyperplasia, and the right superior and inferior and the left inferior parathyroid glands were resected. The left superior parathyroid gland, its weight estimated at about 300 mg., was preserved and the patient was apparently cured. Black[20] has since published in monograph form his large experience with hyperparathyroidism

Nevertheless, one should be most hesitant in making the diagnosis of primary hyperplasia, lest normal parathyroid glands be removed and an adenoma overlooked. Where primary hyperplasia is encountered as it will be occasionally Albright[3] recommends partial resection of the large parathyroid glands, leaving perhaps 200 mg. of hyperplastic tissue

POSTOPERATIVE CARE. *Tetany* The problem most likely to arise following removal of a functioning adenoma is hypocalcemic tetany This is not necessarily due to true hypoparathyroidism, since the serum phosphorus level may be even lower than that present preoperatively The tetany is due in considerable measure to massive recalcification of demineralized bones and hence it is most likely to occur in patients with

marked bone changes[36] To prevent tetany one may need to give calcium by both the oral and the intravenous routes

The *prognosis* following removal of the adenoma depends upon the state of renal disease and function (see patient B L, below) Unfortunately, a large percentage of the patients have advanced renal damage due to renal stones with associated pyelonephritis The removal of the adenoma in these patients may come too late to permit reversal of the advanced renal disease and, indeed, most patients with a parathyroid adenoma eventually die of renal failure On the other hand, if the adenoma is diagnosed early, before renal damage is sufficiently far advanced, the prognosis is excellent

PARATHYROID CLINIC CASE STUDIES *Case 1 Adenoma with renal stones but without demonstrable bone lesions.* B L, a 33-year-old housewife, was well until she developed "pus in the urine" during a pregnancy in 1954 This was successfully treated, and she had no further trouble until March 1956, when she began to have back pain associated with urgency and nocturia (four to five times) Her local physician discovered bilateral kidney stones, and she was admitted to the University Hospital on August 13, 1956, for study She was 5 months postpartum and was lactating

Physical examination revealed no pertinent positive findings Specifically, no mass was detected in the neck, nor were the kidneys palpable

Roentgen studies showed bilateral kidney stones with additional calcinosis (Fig 230) The staghorn calculus on the right was associated with almost no excretion of the intravenously injected Urokon There was reasonably good visualization of the left renal pelvis on intravenous pyelography, though stones were present on this side as well

A bone survey demonstrated no cystic or other lesions that might be due to hyperparathyroidism

Laboratory data were diagnostic Whereas the renal stones might have been due to any number of causes, careful analyses of plasma calcium and phosphorus levels and of [u]rinary calcium excretion indicated tha[t] patient had primary hyperparathyroi[dism] In Figure 231 it may be seen that preo[pera]tively the serum calcium level ranged [from] 14 to 16 mg per 100 cc and the serum p[hos]phorus level from 2 to 3 mg per 100 cc [The] urinary calcium excretion (on a low cal[cium] diet) was above 300 mg per 24 hours on [...] separate occasions—and during one 24-[hour] period it was almost 500 mg The total se[rum] protein level was 6 7 gm per 100 cc [...] these calcium and phosphorus values, t[aken] together, were strongly suggestive of [pri]mary (nonrenal) hyperparathyroidism [The] alkaline phosphatase level was 2 5 Bodan[sky] units, which was in accord with the abs[ence] of demonstrable bone changes There is [in]creasing confirmation that the elev[ated] alkaline phosphatase level of von Reckl[ing]hausen's disease is due to the bone invo[lve]ment rather than to the increased amount [of] parathyroid hormone *per se*, as noted

The blood nonprotein nitrogen (NP[N]) was 22 mg per 100 cc

The first operation, exploration of [the] neck, was performed on September 14, 19[56] A 1 5 by 2 cm parathyroid adenoma [was] found adjacent to the left lower pole of [the] thyroid (Fig 232) The blood supply of [the] yellowish-brown tumor was clearly deri[ved] from the inferior thyroid artery, and excisi[on] was easy Frozen section confirmed the dia[g]nosis of parathyroid adenoma

The immediate postoperative course w[as] uneventful Referring again to Figure 2[31] one may note that the serum calcium le[vel] fell to within normal levels promptly, t[he] urinary calcium excretion declined to le[ss] than 200 mg per 24 hours, and the seru[m] phosphorus level stabilized at about 3 m[g] per 100 cc

A second operation was performed o[n] January 29, 1957, and the staghorn ren[al] calculus on the right was removed Second[ary] hemorrhage occurred around the ne[phrostomy] tube postoperatively, but this re[sponded] satisfactorily to conservativ[e] management At this time the NPN wa[s]



Fig 238 Parathyroid adenoma (Patient B L, see text) *Above* The smaller arrow indicates the parathyroid adenoma the large arrow indicates the lower pole of the left thyroid lobe *Below* Microscopic appearance of the tumor

20 mg per 100 cc serum creatinine 0 8 mg. per 100 cc serum calcium 10 mg per 100 cc, and serum phosphorus 3 5 mg. per 100 cc.

Comment This patient exhibited most of the more common problems met in primary hyperparathyroidism Renal stones, a more frequent complication by far than osteitis fibrosa cystica led to the laboratory studies which established hyperparathyroidism as the underlying etiology of her disease. Al

though renal failure due to nephrocalcinosis and nephrolithiasis had not yet occurred, it could have been expected to do so had the parathyroid tumor not been removed This is the most frequent cause of death in this condition—that is, renal failure due to chronic infection and calculi As is usually the situation, the patient had doubtless had the disease for several years The prognosis is determined by the amount of kidney damage that has occurred before the calcium metabolism is restored to normal by correction of the hyperparathyroidism

Case 2 Adenoma with massive bone involvement but without true renal calculi, pancreatitis, far advanced emphysema, with fatal postoperative pulmonary insufficiency. E H, a 69-year-old retired Pentecostal Holiness preacher, was well until about 1952 when he began having pains in his heels and feet, which gradually came to involve most joints In 1953 roentgen studies were made which showed "malignancy" of the distal portion of the left femur; "palliative" x-ray therapy was given to this lesion but, to the surprise of many, he did not proceed to die He did lose considerable weight, and he developed increasing shortness of breath However, the most striking feature of all was a marked shortening in stature Specifically, he had bought a well fitted tailor-made suit, but little more than a year later he called his wife's attention to the fact that the coat, which was of the correct length originally, now reached almost to his knees Despite a conscious effort to maintain good posture, he had become quite stooped ("my back's bent") The skeletal pain continued, and episodes of dizziness appeared. Marked weakness enforced limited activity

He was admitted to the University Hospital for study on December 17, 1956 Among the tentative diagnoses entertained on the medical service were primary hyperparathyroidism, Paget's disease (of bone), multiple myeloma, osteoporosis of nonspecific origin, and metastatic malignancy

Physical examination revealed a small, markedly kyphotic gentleman who was well oriented, alert and smiling, but whose ph ical power was greatly diminished He co walk only with canes and assistance T thorax was round and "emphysematou and his neck appeared to have sunk into t thoracic inlet, like that of a turtle It w obvious that pulmonary function was a limited by the contour and fixation of t thoracic cage, regardless of what metasta pulmonary calcinosis had occurred Furth more, the neck was so shortened that ex sure at operation for parathyroid adeno would be difficult There was dull tendern over most bones, and sharp tenderness o one rib, this finding was subsequently e plained when a recent pathologic fractu was demonstrated

Roentgen studies showed generalized d mineralization of the skeleton, with mark shortening of the spine (Fig 233) The "ou side" films made in 1953 were obtained, a the increase in bone involvement was stri ing No renal calculi were visualized, thou a very limited excretory function of bo kidneys was apparent from the intraveno pyelogram

Laboratory data were virtually dia nostic The total serum protein level was 5 gm per 100 cc, serum calcium 16 8 mg p 100 cc (8 4 mEq per L), and serum pho phorus 2 6 mg per 100 cc The one di turbing feature was that the 24-hour ur nary calcium excretion on a low calcium di was only 168 mg on one occasion and on 189 mg on another It should have bee higher, it was felt, if a parathyroid adenom were present—but at the same time it wa realized that diminished calcium reserve and diminished renal function might hav reduced the amount of calcium that could b excreted, certainly the elevated blood cal cium level was affording the renal tubule a high enough gradient

The alkaline phosphatase level was 40 35, and 37 Bodansky units on three separat occasions, respectively Moreover, the leve had been measured in 1953 at the first hos pital and had been 4 units, though serum calicum levels at that time had been 13

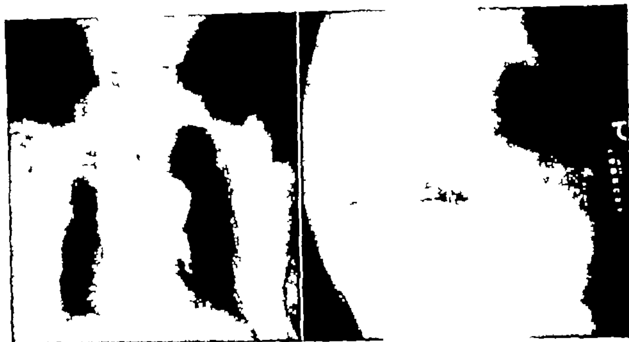


Fig 233 Hyperparathyroidism (Patient E H) Skeletal deformity emphysema and marked shortening in stature Note the greatly increased posteroanterior (P A) diameter of the bony thorax (see text)

and 12.8 mg. per 100 cc. and serum phosphorus levels 2 0 and 2 6 mg per 100 cc Clearly, the original "malignant lesion of the femur had been associated with diagnostic serum calcium and phosphorus values but their significance was not appreciated. The fact that the serum alkaline phosphatase level was only 4 units in 1953, with only one bone cyst, and repeatedly above 35 units in 1956 reflected the great increase in the extent of the bone disease.

The blood urea nitrogen (BUN) had been 38 mg. per 100 cc in 1953 The NPN level was 31 mg. per 100 cc in 1956 and the serum creatinine 1 9 mg. per 100 cc The plasma "CO_2" was 20 mEq, and it was felt that this represented mild renal acidosis There was a fixed low urinary specific gravity and the phenolsulfonphthalein (PSP) excretion was 7 per cent in 15 minutes and 13 per cent in 60 minutes, a total of 20 per cent in 1 hour (a low value indicating limited renal function)

At operation (cyclopropane-ether anesthesia) on January 15 1957 a collar incision was made and the thyroid exposed Search on the left disclosed one small parathyroid Next the right side was explored and buried in the connective tissue between the esophagus and the common carotid artery on the posterior aspect of the right thyroid lobe was found a mass that measured 3 5 by 2 5 by 1.5 cm. before sectioning by the pathologist. The frozen section diagnosis was that of parathyroid adenoma

The postoperative course was unsatisfactory almost from the beginning, due to respiratory insufficiency Intravenous calcium gluconate was given intravenously, and at no time did signs of hypocalcemic tetany develop, nor did the serum calcium level decline below the normal levels it fell to within 24 hours following operation The 24-hour calcium excretion 3 days after operation was 30 mg., a very low value Yet, the serum phosphorus level did not rise

Within 24 hours of surgery, marked respiratory difficulty with hyperventilation and a feeling of suffocation had appeared Cyanosis and, at times Cheyne-Stokes respiration were present. Tracheostomy was performed to diminish respiratory dead space Oxygen therapy was tried but was not particularly helpful and was abandoned because of the hazard of such therapy in certain emphysematous patients Aerosols were employed to diminish the viscosity of the large amounts of viscid tracheobronchial

secretions which were periodically removed with catheter suction Unfortunately, respiratory efficiency did not improve, and the patient became gradually exhausted by the constant respiratory effort Despite all measures, he died quietly on the sixth postoperative day The cause of death appeared to all observers to be that of respiratory insufficiency, due largely to diffuse emphysema, diminished thoracic mobility, and bronchopneumonia

Autopsy disclosed bronchopneumonia and pulmonary emphysema, mild cardiac enlargement, mild to moderate *pancreatitis*, and "parathyroid nephritis" It was considered that the pathologic findings were compatible with the clinical diagnosis of respiratory insufficiency as the primary cause of death Postoperative blood pH measurements would have been helpful in further evaluating the possibility of acidosis, a condition that was suggested by the low plasma carbon dioxide combining power values The urine output was consistently good

Comment This man exhibited the classic osteitis fibrosa cystica described by von Recklinghausen The bone cyst and typical serum calcium and phosphorus values should have resulted in a correct diagnosis of hyperparathyroidism 4 years earlier, in 1953 However, the disease is not so common that one is disposed to think of it routinely, unless it is suspected in the presence of any cystic bone disease or renal stone The marked bone involvement produced a sharp elevation of the alkaline phosphatase level

In retrospect, despite the very short neck and difficult exposure, local anesthesia might have been preferable from the standpoint of minimizing pulmonary irritation in a man who already had a seriously diminished pulmonary functional capacity This choice was discussed preoperatively but was unfortunately not elected

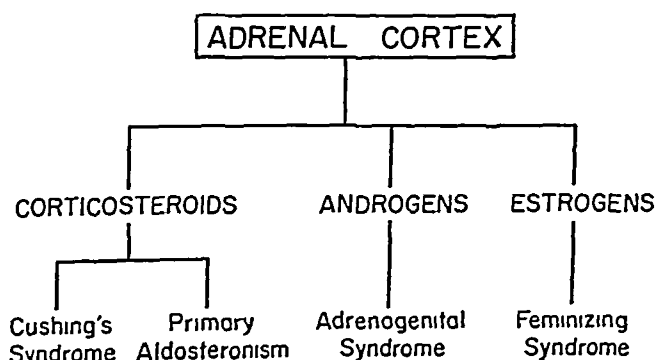


Fig 234 Hormones of the adrenal cortex the syndromes produced by hypersecretion

The Adrenal Cortex

The physiology of the adrenal cortex embraces a host of activities, and many of these have been touched upon in other sections The pre-eminence of the cortical steroids in the metabolic response to operation is due to their effects on the processes of protein-*fat-carbohydrate utilization*, fluid balance, blood pressure regulation, immune response, and many other functions Therefore, it is not surprising that excessive adrenocortical activity results in a very diffuse or complex clinical picture The chemistry of the adrenal steroids continues to unfold[41]

The facets of adrenocortical physiology will be considered in the following order (1) hyperadrenocorticism, (2) adrenalectomy for essential hypertension and for malignant neoplasms, (3) preoperative and postoperative care, including signs of acute, subacute, and chronic adrenocortical failure, (4) adrenocortical hormones in surgical treatment

Hyperadrenocorticism

This term refers to the clinical effects produced by excessive amounts of one or more of the hormones[107] of the adrenal cortex Greatly simplified, oversecretion of hydrocortisone-like steroids produces Cushing's syndrome Excessive secretion of aldosterone results in aldosteronism Excessive secretion of androgenic hormones results in the adrenogenital syndrome Lastly, excessive secretion of adrenal estrogens may produce feminization in the male These *syndromes* are shown in Figure 234 However, there is much overlapping In general, the hydroxycorticoid family (of which hydrocortisone represents about 85 per cent of the total secretion) is derived from the zona fasciculata

or middle zone, aldosterone is probably derived from the zona glomerulosa or outer zone, and the adrenal androgens are probably derived from the zona reticularis or inner zone (Fig. 235)

Let us now consider the more clearly delineated of the several clinical syndromes derived from excessive secretion of the different adrenocortical steroids The clinical findings depend primarily upon the chemical formula of the hormone or hormones that are present in excess, but the physical appearance of the patient is further modified by age and sex. Moreover, the hyperadrenocorticism may result from adrenocortical hyperplasia or tumor, or from steroid therapy In these respects hyperadrenocorticism is comparable to hyperthyroidism due to diffuse goiter toxic adenoma, or thyroid substitution therapy There is further similarity, in that diffuse hyperplasia of either organ may result from excessive secretion by the anterior pituitary of the respective tropic hormones, TSH and ACTH In this instance most of the functioning tissue of each lobe of the thyroid or of each adrenal must be excised to reduce hormonal secretion to normal In contrast the functioning solitary adenoma of either the thyroid or the adrenal is largely autonomous (not under the control of the pituitary) and, therefore simple removal of the adenoma usually effects a cure unless in the case of the adrenal the lesion is malignant

In the presence of hyperplasia the adrenal glands tend to maintain their normal configuration, but in the presence of tumor the normal configuration is usually lost.

Cushing's Syndrome

The pathophysiologic changes encountered in Cushing's syndrome are caused by the excessive secretion of glucocorticoids and can be reproduced in some measure by the administration of excessive amounts of cortisone or hydrocortisone over a prolonged period While there may be considerable hirsutism in this syndrome, it is more generally distributed and usually less masculine

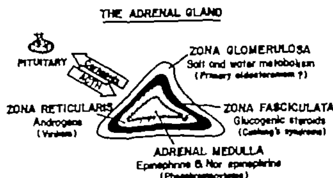


Fig 235 Functional anatomy of the adrenal gland and its reciprocal relationship with the anterior pituitary Aside from a degree of autonomy of the zona glomerulosa, the adrenocorticotropic hormone (ACTH) stimulus is required for normal adrenocortical activity Conversely an excess amount of circulating corticosteroid as during cortisone therapy tends to suppress the release of ACTH by the pituitary Adrenocortical hyperplasia is due to an excessive secretion of ACTH by the pituitary but this hypersecretion must be mediated through the adrenal cortex to produce Cushing's syndrome or the adrenogenital syndrome. The adrenal medulla is not under the control of the pituitary and is not essential for life

in distribution than in the adrenogenital syndrome There is commonly a "buffalo" type of obesity, a plethoric appearance with a 'moonlike' face, purple striae of the thighs and abdomen, ecchymoses, and a wasting of the muscles of the extremities and elsewhere (Fig. 236) Hypertension is likely, and amenorrhea is common in women. Further investigation reveals osteoporosis and perhaps polycythemia and hypokalemic alkalosis An elevated blood sugar level and a diabetic type of glucose tolerance curve are frequently found. These patients may have definite mental aberrations and a fairly definite type of psychosis may develop, as a somewhat different abnormal mood is observed in the patient with Addison's disease.

DIAGNOSIS OF CUSHING'S SYNDROME.[1] *History and physical examination* The history and the physical examination may suggest endocrine abnormality and prompt further studies (Figs 236 to 238) However, the disease may come on most insidiously and, while to a new physician the clinical picture might at once suggest Cushing's syndrome, the physician who has followed the patient from the first nonspecific complaints is often



Fig 236 Cushing's original case Note abdominal striae, truncal obesity, and hirsutism of lip (From CUSHING, H The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism) Bull Johns Hopkins Hosp, **50**. 137, 1932)

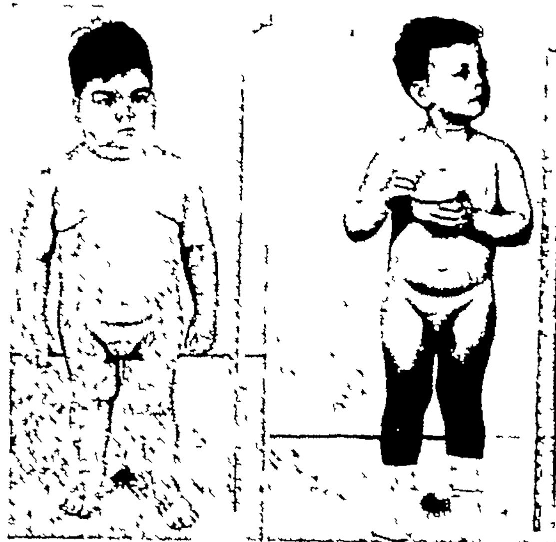


Fig 237 Case study, Cushing's syndrome in child Patient J S was markedly obese, hypertensive, mildly diabetic, and had an insatiable appetite *Left* Appearance on admission *Right* Appearance 5 months after resection of most of each adrenal (From ROSE, E K, ENTERLINE, H T, RHOADS, J E, AND ROSE, E Adrenal cortical hyperfunction in childhood Pediatrics, **9** 475, 1952)



Fig 238 Cushing's syndrome This obese man with wasted legs had a malignant tumor of the right adrenal with hepatic metastases Note the abdominal striae and ecchymoses Cortical hormones promote fat deposition but lean tissue wastage—"the weak fat man" (patient J H, see text)

blind to the marked changes that have developed before his very eyes Under these circumstances, confirmatory laboratory studies may not be requested So it was with patient J H, whose case is described below

Laboratory studies It has been seen that the glucose tolerance curve is often abnormal, and that hypokalemic alkalosis and polycythemia may be found Even so, in our experience these data have been less helpful than the actual determination of plasma and urinary steroid values The *urinary excretion of both corticoids and 17-ketosteroids* is usually elevated, though the increase in corticoids predominates Normal values must be established for the individual laboratory We have used a modification of the method of Heard and Sobel for corticoid determinations, and the urinary excretion in normal subjects has ranged from 5 to 8 mg per 24 hours The standard Zimmerman reaction for 17-ketosteroid measurement gives values which normally range from about 10 to 20 mg per 24 hours in men and

from about 7 to 15 mg. per 24 hours in women. Children have lower values.

Plasma hydrocortisone levels and their response to ACTH afford important additional information. In our laboratory, normal plasma hydrocortisone levels range from 5 to 10 μg (gamma) per 100 cc of plasma The response to ACTH is performed as follows 20 units are infused at a constant rate over a 4-hour period, and a blood sample is drawn at the termination of the infusion In normal individuals the plasma corticoid level is less than 30 mg. per 100 cc, in Cushing's syndrome the level is usually much higher than this

As will be more fully presented subsequently, most cases of the adrenogenital syndrome can be diagnosed by the decline in the level of 17 ketosteroid excretion following cortisone or hydrocortisone administration. This does not readily occur in Cushing's syndrome to permit differential diagnosis between hyperplasia and tumor Fortunately, however, this is not of great importance in Cushing's syndrome for whether the disease be due to tumor of the adrenal or to hyperplasia surgical management is indicated.

Finally it should be noted that in some cases of Cushing's syndrome the excretion of corticoids and 17 ketosteroids is within the upper range of normal and no definite increase in hormonal secretion can be demonstrated. This is particularly true of patients who exhibit only a generalized hirsutism, for many hirsute individuals have essentially normal endocrine function. The basic hair pattern of the individual is genetically determined and patients of different racial origin vary widely with respect to the amount of hair which may normally be expected Yet in addition to hereditary factors the amount and distribution of body hair is also influenced by corticoids androgens and estrogens Wilkins[107] has emphasized that sexual hair—facial pubic and axillary—which is influenced particularly by androgens and estrogens should be considered apart from other body hair Again, as noted above, generalized hirsutism is a feature of Cushing's syndrome, but there is not necessarily a marked increase in hair

MANAGEMENT OF CUSHING'S SYNDROME. *Medical therapy has not been satisfactory* in the management of Cushing's syndrome, a disease which is incompatible with normal longevity *Surgery is required* The best results are obtained when a benign tumor is found and excised, unfortunately, many of these tumors are malignant, highly so Much more frequently the condition is due to bilateral adrenocortical hyperplasia and here the surgeon must choose between total and subtotal adrenalectomy The disadvantage of total adrenalectomy is that although hyperadrenocorticism is abolished, permanent adrenal absence is produced and thereafter the patient must forever remain under close and competent medical supervision The disadvantage of subtotal adrenalectomy is that the tissue remaining may hypertrophy or exhibit true hyperplasia and again produce Cushing's syndrome

What incision to use? Unless a tumor can be demonstrated by palpation, by plain soft tissue roentgenography, by intravenous or retrograde pyelography or by roentgen study using retroperitoneal oxygen insufflation, it is difficult if not impossible to distinguish preoperatively between adrenocortical hyperplasia and adrenocortical tumor If tumor on which side is it situated?

If the site of a tumor can be identified preoperatively we often use the thoracoabdominal incision avoiding the anterior abdominal fat. If a tumor has not been identified at the time of operation we make a transverse upper abdominal incision so that any contingency can be dealt with One may explore through a short transverse incision near the midline and this can then be extended to one side if a tumor is palpated, or it can be extended to both sides if adrenal tissue is to be resected bilaterally for hyperplasia. All tumors are removed by adrenalectomy on the involved side We most often deal with bilateral hyperplasia by resecting all of the right adrenal and leaving only a

thumbnail size remnant surrounding the central vein on the left, where drainage is to the easily accessible renal vein Meticulous exposure is more difficult on the right, where drainage is directly into the inferior vena cava beneath the liver The transverse abdominal incision is readily converted to a thoraco-abdominal incision, if required

If a sufficient amount of adrenal tissue is removed, the female patient will in the course of the next few weeks resume her menses, the pathologic obesity will disappear, and normal strength and libido will return

CASE STUDIES The following two patients present instances of Cushing's syndrome The first subject, a woman, had bilateral hyperplasia and was temporarily "cured" by almost total adrenalectomy The second subject, a man, had a right adrenocortical carcinoma that was found to have metastasized to the liver, and he subsequently died

Cushing's syndrome due to adrenocortical hyperplasia (This case was diagnosed and referred by Dr J Manning Hudson, Jackson) M N , a 23-year-old housewife was in her usual state of health until 1949, when she began to gain weight and noticed an increased growth of hair on her face, legs and abdomen, and between the breasts The pubic hair assumed the male escutcheon and all hair became darker, as did the skin Over the next 6 years her face became more round, *weakness* developed despite weight gain, and headaches were increasingly frequent Her sexual desire declined, but menstrual periods remained essentially normal

Physical examination at the time of her admission to the University Hospital on August 8, 1955, revealed an obese, mildly hypertensive young woman with a ruddy skin over a moon-face There was moderate, generalized hirsutism, but no significant voice changes Striae were not present, the clitoris was not enlarged, and supraclavicular fat pads were not prominent

Roentgen studies revealed no soft tissue mass and the kidneys were not displaced The sella turcica was within normal limits and no osteoporosis was noted

Laboratory data disclosed the following fasting blood sugar (FBS) 85 mg per 100 cc , essentially normal glucose tolerance curve, NPN 24 mg per cent, virtually normal peripheral blood count *The 24-hour 17-ketosteroid excretion was 30 8 mg , approximately three times the normal level* Corticoid measurements were not yet available in the newly opened hospital

The diagnosis was considered to be that of Cushing's syndrome This was supported by a compatible history, physical examination, and the elevated excretion of 17-ketosteroids

Operation was performed on August 22, 1955, through a transverse upper abdominal incision No tumor was found in either adrenal area, and both ovaries were normal to palpation (an arrhenoblastoma had to be excluded) The left adrenal gland was almost twice the size of the right, grossly and by subsequent weighing Nevertheless, having once had recurrence of an adrenogenital syndrome in a patient whose enlarged adrenal only was removed, I removed approximately 95 per cent of both adrenals, leaving the remnant just around the emerging central vein

Postoperatively she did well on 100 mg of cortisone intramuscularly every 6 hours, having also received 100 mg immediately prior to operation The fever promptly rose to 102° F and the pulse rate to 120 However, at no time were we seriously concerned about her, and within 72 hours the vital signs had returned to preoperative levels The ACTH and cortisone were gradually discontinued, with the plasma sodium and NPN levels stabilized at normal levels

Even before discharge from the hospital on September 3, she stated that she was stronger than before operation

She was seen 3 months later and felt well The obesity had diminished, she felt she had normal strength, and libido had returned Interestingly, as of the present

writing (March 1958), she has again begun to have symptoms of weakness and easy fatigue but there is no physical or laboratory evidence of disease Regeneration[15] or hypertrophy of remaining *adrenal tissue* does occur

Comment on case This patient presented a *relatively early case of Cushing's syndrome*, and many of the features of the "full blown" disease were absent. Specifically, she had no striae, ecchymoses, amenorrhea, diabetes plasma electrolyte derangements, osteoporosis, or polycythemia. However most diseases have an initial period, brief or protracted, during which signs and symptoms are minimal Adrenocortical hyperfunction characteristically pursues an insidious course, but it usually increases progressively nonetheless This young woman had had definite evidence of adrenal hyperfunction for at least 6 years, but the stage of the disease was still not an advanced one at the time of successful surgery The next patient presented as florid a picture as one could wish.

Cushing's syndrome due to adrenocortical carcinoma J H *a 58-year old machinist* had always been fat (weighed 300 lb), but considered himself to be in good health until January 1955 At that time he consulted a company physician for rather vague symptoms and was told he had a goiter but that treatment was not necessary Things went along through the spring and summer and, while he did not feel really well neither did he feel really sick. He continued working full time The first positive finding of historic note came in August of that same year, when numerous purplish blood spots *(ecchymoses) broke out on his* extremities and particularly on his forearms. Furthermore bleeding from abrasions at work appeared to be more difficult to control than before and the skin over the ecchymoses was perforated with great ease

In September there began attacks of back pain which afterward continued intermittently Cystoscopy was performed and a diagnosis of polycystic kidneys was made *Hematuria occurred from time to time.*

From this time on he was not able to work consistently, chiefly because he was weak. *He was frequently nauseated and* at times, upon arising from lying down, he felt that 'something slipped downward" in his abdomen. This sensation was associated with dyspnea, which always gradually subsided in a few minutes and he felt all right again

He realized that he was becoming more and more *depressed* and *moody* This was unnatural, and his family was concerned

On admission to the University Hospital on March 3, 1956 for study his weight had declined from the 'healthy" value of 300 lb he now weighed 230 lb The chief complaints were still back pain, hematuria, and intermittent fever—plus a *profound weakness* Even his voice had become weak. This distressed the patient since both he and his friends thought that a man so fat could not be sick and should not be so weak His family knew he was sick though, for he had never before been one to complain. The intern's *work up began with "a strange and* complex story "

Physical examination revealed a classic picture of Cushing's syndrome though by *no* means all were agreed on this point. The surgical service was consulted regarding the nodular goiter and the consultant wrote as follows

I believe there are three items upon which I might comment

1 Fundamental cause of weakness—possibly Cushing's syndrome (purplish striae, ecchymoses, truncal obesity etc) Suggest usual studies to rule in or out (glucose tolerance test, corticoids and 17 ketosteroids)

'2 *Nontoxic nodular* goiter confined to left lobe—larger than it appears at first and displacing trachea slightly to right.

'3 Lower extremities—*dependent rubor* of feet with tropic changes in skin and toenails Rt femoral (artery) barely palpable

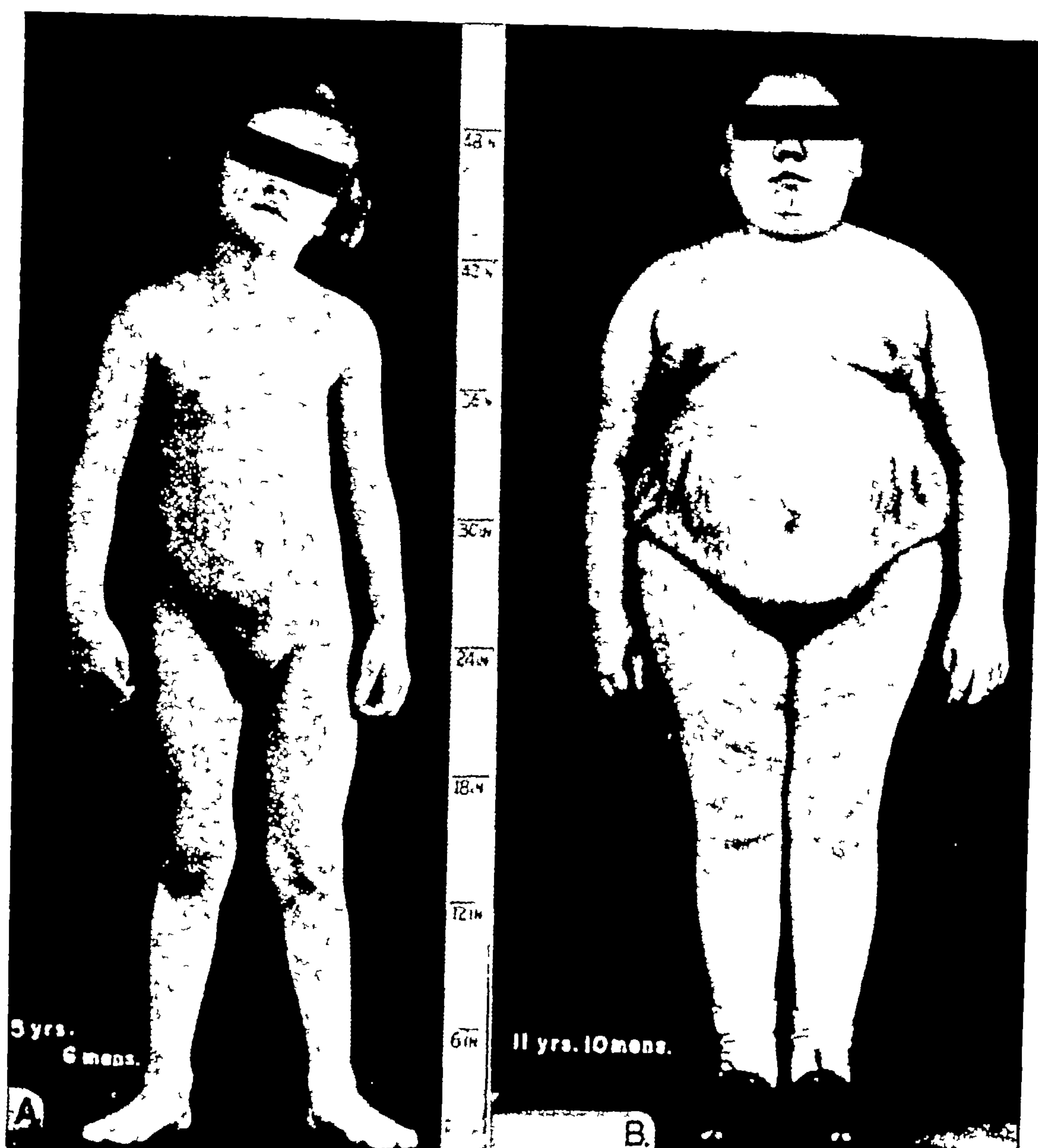


Fig 240 Comparison of adrenogenital syndrome (*left*) with Cushing's syndrome (*right*) in girls (From Albright, F Cushing's syndrome Harvey Lect, **38** 123, 1942–1943) The adrenogenital syndrome, caused by adrenal androgens, produces masculinization in females and precocious puberty in males The condition is compatible with normal longevity In contrast, virilism is not a prominent feature of Cushing's syndrome, a generalized metabolic disorder, here the muscular growth and strength characteristic of the adrenogenital syndrome are replaced by muscle wasting, weakness, and fat deposition Striae, ecchymoses, diabetes, and hypertension are common findings in this disease which, if severe, is incompatible with normal longevity Both the adrenogenital syndrome and Cushing's syndrome may be caused by adrenocortical hypersecretion resulting from either tumor or hyperplasia

quite striking, if in a boy or girl or in the adult female The pubic hair is masculine in distribution, the voice is coarse and often deep, and adult females must usually shave —hence the bearded lady of the circus ' In contrast to the weakness of the patient with Cushing's syndrome (a profound metabolic disorder affecting most body processes), the woman with the adrenogenital syndrome is strong and may anticipate a normal (if unhappy) life span

In children with the adrenogenital syndrome the physical manifestations vary according to the sex of the patient and the age of onset If adrenal hyperplasia occurs in the male child prior to birth, macrogenitosomia precox may be present (precocious development of body and genitalia) As noted,

yperplasia appears after birth, sexual ocity and accelerated general body de- pment may be observed during child 1. If overproduction of androgens by the enal cortex occurs in the female *in utero*, condition gives rise to a rather uniform e of female pseudohermaphrodism At h the clitoris is found to be hypertro- ed, resembling a hypospadial penis and nd ventrally by fibrous cords extending kward from the undersurface. The con on is almost always due to hyperplasia en the adrenogenital syndrome develops he adult female, however, the possibility ts being due to a tumor is a significant one l this possibility should be excluded at e

The adrenogenital syndrome may of irse be due to androgen secreting ovarian nors such as adrenal rests or true ovarian henoblastomas It can also be produced excessive doses of androgen therapy in nales as in the management of metastatic east cancer

DIAGNOSIS OF ADRENOGENITAL SYNDROME. It s been pointed out that if the condition is esent at birth or appears during childhood, s almost surely due to adrenocortical hy rplasia If it develops in a previously nor il menstruating woman then the possi lity of adrenocortical tumor must be riously considered. Therapeutically, it is portant to distinguish between the two, r *conservative* therapy with cortisone or drocortisone may be used for the suppres- on of androgen production by hyperplastic gans, tumors require operation Fortu itely, Wilkins and his group[104] described a eans of doing this. If the elevated urinary cretion of 17 ketosteroids declines on cor sone therapy the condition is very likely be due to hyperplasia (Figs. 241 and 242) there is no significant effect, tumor must e excluded by operation The exogenous ortisone suppresses the endogenous secre- on of ACTH and androgen production de- lines It has been shown that the secretion f ACTH is increased in patients with the drenogenital syndrome due to hyperplasia



Fig 241 Case study adrenogenital syndrome Enlarged clitoris and hyperplastic adrenal in 14 year-old girl For 6 or 8 years the mother had noted an enlarging clitoris The girl had become stocky her forehead hairline had receded (Fig 251) and her voice had deepened. Menses had not begun breast development was absent and pubic hair exhibited the male escutcheon. Shown below are the nodular adrenal gland removed from the patient at surgery (only one gland was enlarged) a normal adrenal gland from another patient and a piece of cardboard cut to the approximate size of the adrenal opposite the hyperplastic one (From HARDY J D *Surgical Physiology of the Adrenal Cortex* Springfield Ill., Charles C Thomas 1955)

Tumors on the other hand, are usually au tonomous and not dependent upon the ACTH stimulus

In virilizing adrenocortical hyperplasia the level of urinary 17 ketosteroid excretion rarely much exceeds 60 mg. per 24 hours this level may be somewhat greater in the presence of a benign tumor, but it may be greatly increased in the presence of a malignant tumor of the adrenal (Figs. 243

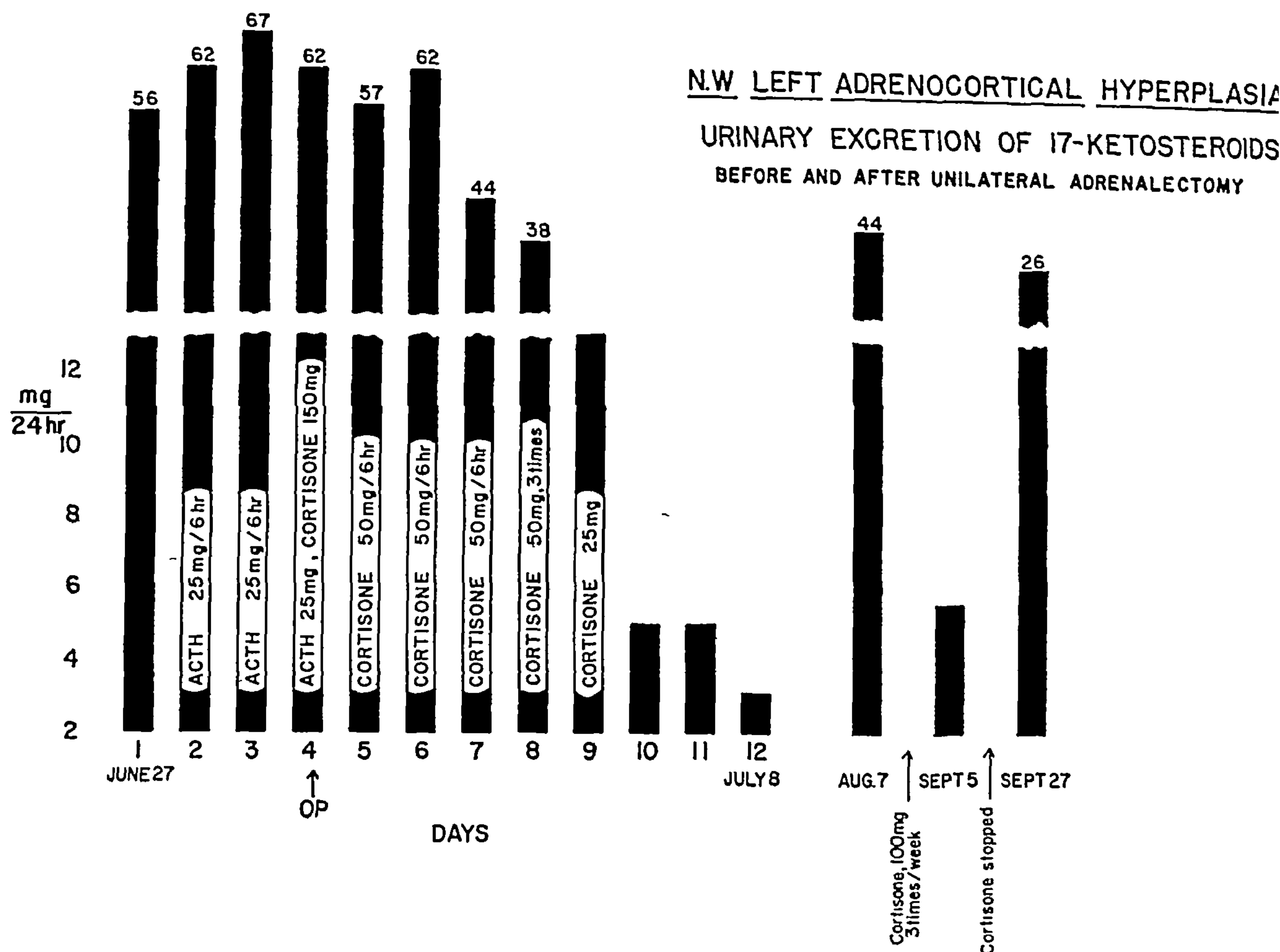


Fig 242 This patient is the one referred to in Figures 241 and 251 She was operated upon prior to the current practice of using corticosteroid therapy to suppress androgen production At surgery the left adrenal was found to be hyperplastic and nodular (Fig 241), but the right adrenal was grossly normal, the left adrenal was removed The ovaries and uterus were hypoplastic but were otherwise not remarkable The parents were advised that hyperplasia of the right adrenal might develop later, and this did occur Note that following removal of the hyperplastic left adrenal the previously elevated excretion of 17-ketosteroids (representing degraded androgens) fell to normal levels on the sixth post-operative day (tenth day of study) However, by August 7 the level had risen again to 44 mg per 24 hours Cortisone suppressive therapy was then started and the 17-ketosteroid excretion fell promptly It was allowed to rise once again by stopping the cortisone temporarily, but thereafter the dosage was maintained This suppression of androgen production permitted gonadotropic hormones to produce feminization (breasts and menses), probably through ovarian estrogen production (From Hardy, J D *Surgical Physiology of the Adrenal Cortex* Springfield, Ill, Charles C Thomas, 1955)

and 244) The production of corticoids is also usually increased, but the production of 17-ketosteroids (androgens) preponderates to produce masculinization, if corticoid production had been preponderant, Cushing's syndrome would have resulted

In addition to the test of the effect of cortisone therapy on 17-ketosteroid excretion, all the other usual measures should be used to exclude tumor

Fractionation of 17-ketosteroids may be helpful For example, it may be difficult to distinguish virilism produced by adrenocortical hyperfunction from that produced by a true tumor of the ovary In general, the alpha fraction is secreted by both the adrenal cortex and tumors of other organs such as the ovary or testis, but the beta fraction is secreted only by the adrenal cortex [65] Normally and in adrenal hyperplasia the beta fraction represents only 5 to 15 per cent of the total excretion, but in the presence of an adrenocortical tumor the beta fraction may be greatly increased

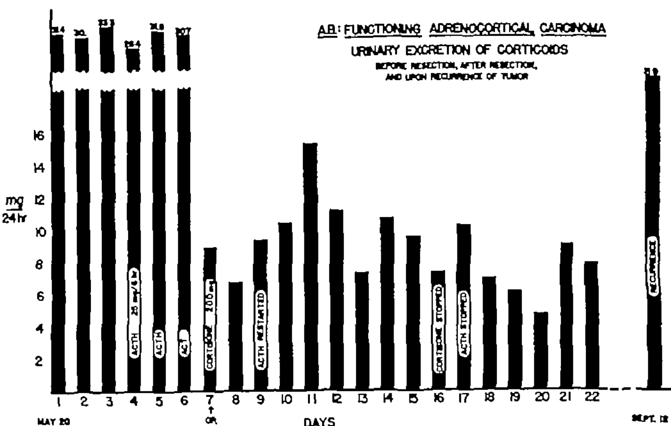


Fig 243 Adrenogenital syndrome due to adrenal carcinoma. Case study This 28-year old married medical secretary had been treated for various complaints for two years until an enlarged clitoris was observed and correlated with a mass in the right upper quadrant. She had an huge adrenocortical carcinoma which was producing excessive amounts of both corticosteroids (corticoids) and androgens (Fig 244) Although androgen production predominated and resulted in the adrenogenital syndrome the corticoid production was also increased as shown above Note that the elevated level of 31 mg per 24 hours (normal, 3 to 8) present preoperatively was not affected by adrenocorticotropic hormone (ACTH) Postoperatively the level fell to normal. On September 12 she returned with liver metastases and the level had risen again to 21.9 mg per 24 hours. (From HARDY J D Urinary steroids in adrenocortical tumor Ann. Surg 138: 765 1953.)

It may be difficult to distinguish *hormonal* from *genetic pseudohermaphrodism* Wilkins[107] has stated that if pubic hair, increased osseous and somatic development and an increase in 17 ketosteroid secretion appear after birth the diagnosis is probably that of adrenocortical hyperplasia. If the enlarged clitoris and other signs of abnormal sexual development have been present from birth, with no pubic hair or increase in 17 ketosteroid excretion, the condition is probably genetic in origin.

SURGERY VERSUS STEROID THERAPY IN ADRENOGENITAL SYNDROMES All tumors are excised because of the danger of malignancy It is still too early to determine whether cortisone therapy will be permanently satisfactory for the management of hyperplasia and in fact, our limited experience suggests that it will not be Nevertheless, at the present time it is our feeling that this therapy should be given a fair trial We have used 200 mg. of cortisone daily for 2 weeks, by which time the excretion of 17 ketosteroids has usually declined and dosage is accordingly reduced. Jailer and his associates[62, 63] studied 26 patients with adrenal hyperplasia and 10 patients with functioning adrenal tumors including instances of both adrenal virilism (adrenogenital syndrome) and Cushing's syndrome A significant fall in urinary 17 ketosteroids was obtained in all patients with adrenal virilism secondary to adrenal hyperplasia and in most instances of Cushing's syndrome due to this disorder In no instance was a fall in urinary 17 ketosteroids

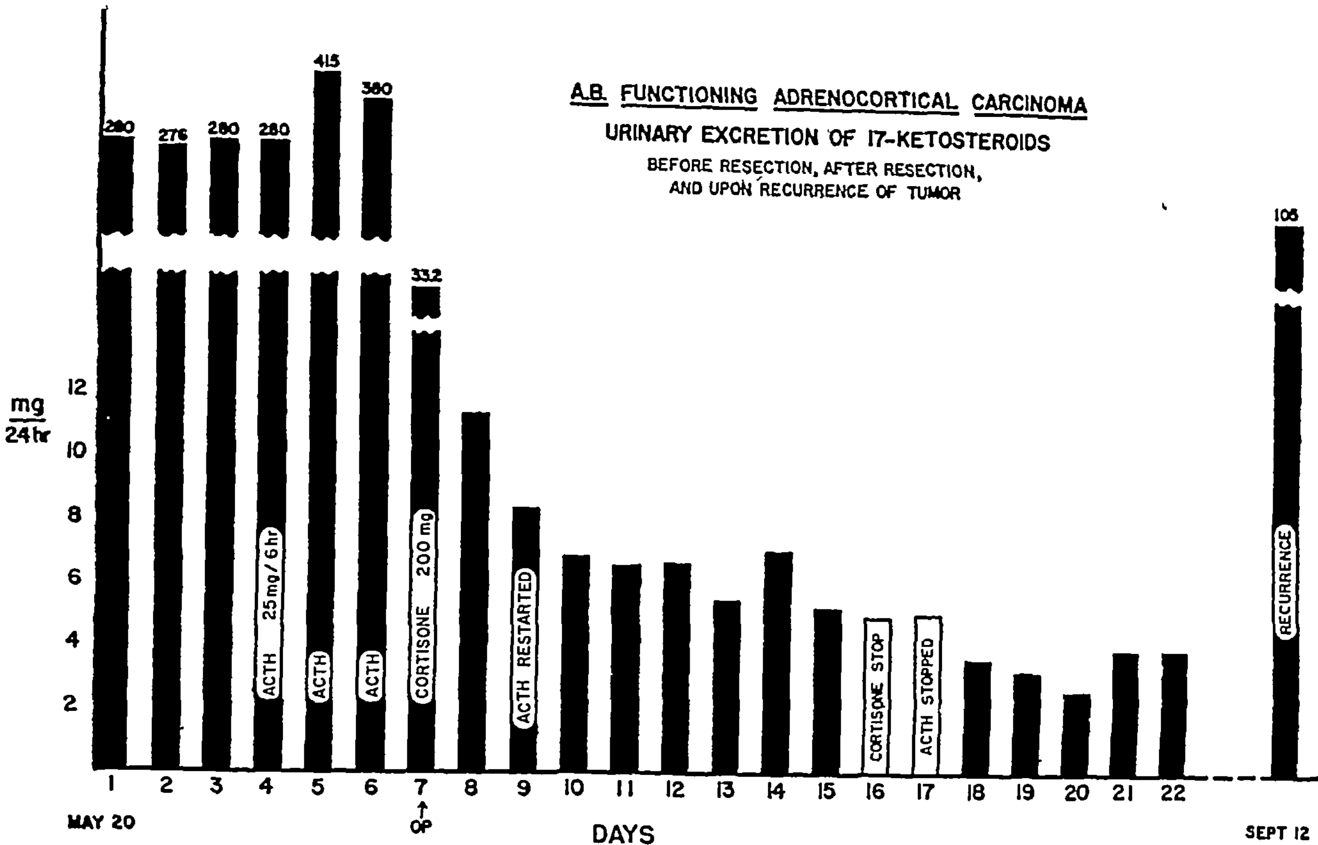


Fig 244 Case study, adrenogenital syndrome due to adrenal carcinoma This patient, who is further described in Figure 243, had a 17-ketosteroid excretion of 280 mg per 24 hours (normal, 10) Surprisingly, the tumor responded to adrenocorticotropic hormone (ACTH) therapy by increasing the excretion to 415 mg per 24 hours, though the corticoid excretion did not change (Fig 243) The level of 17-ketosteroid excretion fell to normal levels immediately following removal of the tumor and to very low levels when the ACTH was stopped on the seventeenth day of the study The ACTH had been given to stimulate the probably atrophic left adrenal—since atrophy is common in the adrenal opposite one which harbors a functioning tumor (in contrast to hyperplasia, as in Figure 241) On September 12 she returned with hepatic metastases, and the level of 17-ketosteroid excretion had risen again to 105 mg per 24 hours Malignant adrenocortical tumors often produce very high rates of steroid secretion, whereas hyperplasia results in intermediate rates (From HARDY, J D Urinary steroids in adrenocortical tumor Ann Surg, **138**. 765, 1953)

obtained in patients with functioning adrenal neoplasms In another instance which was brought to our attention, there was a reduction in 17-ketosteroid excretion following the administration of cortisone orally, but the level did not decline entirely to within normal limits At operation it was found that the patient had an arrhenoblastoma of the ovary, a true ovarian tumor which also secretes androgens It would appear that in this instance the oral administration of cortisone had diminished the secretion of 17-ketosteroids by the adrenals, but that it had not reduced the androgens elaborated by the ovarian tumor Again, if the urinary excretion of 17-ketosteroids does not decline to within normal limits, the patient should be explored for the possibility of a tumor

Our experience with only a few such patients has been that more and more cortisone is required and that initial improvement is difficult to maintain In one teen-age girl, for example, feminization was achieved initially, but this subsequently regressed even under much higher cortisone dosage In some patients, and particularly in some infants *in utero*, the androgen-producing cells of the zona reticularis may become so hyperplastic as to crowd out the cells of the zona glomeru-

losa and the zona fasciculata, which secrete the life-maintaining corticoids Adrenocortical failure and death may ensue in the neonatal period. This circumstance was reported by McQuarrie and his associates[79] and we ourselves have observed a female infant who was hermaphroditic at birth and died of adrenocortical failure a day or so later

The case now to be presented emphasizes many of the problems associated with adrenal virilism

Case study Adrenogenital syndrome (virilism, pseudohermaphrodism) due to bilateral adrenocortical hyperplasia E. H , a 43-year-old divorcee, had been extremely 'passionate since the age of 6 and had masturbated frequently throughout the ensuing years in search of relief from the driving libido The clitoris had been large since she could remember, the voice husky, the increased body and sexual hair coarse, and she shaved regularly She had menstruated only three times in her life, this at the age of 31 following a course of pill therapy for 1 year

She had always been rather big and stocky and had stopped growing at the age of 12 In 1947 she had married but her sexual desire was so great and so incessant that her husband soon left her Since that time she had occasionally worked but for the most part she had drifted restlessly from one relative to another, moving frequently

In 1951 she was operated upon in Mobile, Alabama and bilateral adrenocortical hyperplasia was demonstrated. However, no adrenal tissue was resected at that time because of the inadequacy of the replacement therapy that would be available to her The 24-hour excretion of 17 ketosteroids in 1954 was reported as 61 mg

Another finding of note was the fact that she had suffered from nocturia (6 to 8 times) for many years.

A niece was reported to be developing evidence of the adrenogenital syndrome, in line with the strong genetic tendency of the disease.

On admission to the University Hospital on January 9, 1955, she exhibited the usual physical signs of virilism that were described above The body hair was wiry, the voice rather deep, the build stocky, the breasts moderate in size, and the clitoris about four times normal size. Blood chemistry studies were essentially normal, but the 24 hour excretion of 17 ketosteroids was 28 mg (average normal, 10 mg)

Since the presence of adrenocortical hyperplasia had been observed by a competent surgeon in Mobile, it was decided to give the patient cortisone therapy to reduce the adrenal androgen production—this by suppressing pituitary function and its secretion of ACTH In this way the life maintaining corticoids were supplied by oral therapy, meanwhile suppressing ACTH which would stimulate the adrenals to secrete not only corticoids but the unwanted androgens as well

This therapy did lower the androgen production to normal levels, in that the 17-ketosteroid excretion declined to 5 9 mg. per 24 hours Yet, the libido was only slightly decreased the patient's headaches were only partially relieved, and she was by no means rehabilitated. Adrenalectomy is still under consideration as of this writing

Comment This patient presents a fairly typical story of the unfortunate girl who has adrenal virilism or pseudohermaphrodism. Since she had had symptoms since the age of 6, the disease was almost surely due to hyperplasia rather than to tumor Suppressive cortisone therapy for this condition has been thus far, disappointing to us, and we are tending once again to be inclined to do subtotal bilateral adrenalectomy True philosophically and theoretically suppressive steroid therapy has great appeal but in actual practice it has failed to work effectively for us. It routinely reduces the 17 ketosteroid output in hyperplasia of course but larger and larger doses of cortisone have been required to maintain the initial response in our limited experience

Primary Aldosteronism

Aldosterone has been isolated only recently.[98] Prior to this it had been appreciated that when all known adrenocortical hormones had been removed from the adrenal brei, there still remained behind in the residue an "amorphous substance" with a marked effect upon salt metabolism. This was aldosterone. This corticosteroid has been shown to have a specific rôle in water and salt metabolism, that is, only fluid balance is affected by aldosterone. One of the glucocorticoids must be supplied for maintenance following complete adrenalectomy. Moreover, while the glucocorticoids have as their major rôle the maintenance of functions other than that of fluid metabolism, most of them also have a sufficient effect on electrolyte metabolism in most patients to maintain health in the absence of other adrenocortical hormones.

In 1955 Conn[34] reported a patient whose clinical features were termed *primary aldosteronism*. The findings consisted of hypertension, muscle weakness, renal and electrolyte abnormalities, and an increased excretion of salt-retaining hormone in the urine.

The plasma chemical change in primary aldosteronism consists of hypokalemic alkalosis and hypernatremia. The condition has usually been due to an adrenocortical tumor secreting increased amounts of an aldosterone-like substance.

It is to be expected that primary aldosteronism will be diagnosed more frequently now that the typical clinical picture and the hormone responsible have been identified. Tumors should of course be removed by adrenalectomy.

Conn and his associates[35] have also described an increase in aldosterone secretion in connection with *familial periodic paralysis*. It appears that the associated retention of sodium may be a pathogenic factor in the electrolyte derangements which characterize this condition, of which a lowered plasma potassium level is a conspicuous feature. This finding is considered to be due to a movement of the potassium ion into the cells. During recovery there was excretion of considerable amounts of sodium but little potassium.

Liddle, Duncan and Bartter[60] have reported evidence for a dual mechanism regulating adrenocortical functions in man. The secretion of glucocorticoids appears to be regulated by ACTH, whereas the rate of secretion of aldosterone is to a considerable extent independent of ACTH. This has, of course, been suspected for some years.

Adrenocortical Insufficiency

The hormones of the adrenal cortex are essential to life, and the absence of at least a minimal supply is reflected in shock.[59] Nevertheless, the rapidity with which circulatory collapse develops is dependent upon whether or not there is complete absence of the hormones, as in total adrenalectomy, or whether a marked but incomplete depletion of hormones exists. Thus, incomplete absence results in *subacute adrenocortical insufficiency* and *chronic adrenocortical insufficiency* (*Addison's disease*).

Acute adrenocortical failure. This picture may be produced by complete or nearly complete adrenalectomy. It may also be seen following the stress of other types of surgery in a patient who has inadequate adrenal function to furnish the normal metabolic stability—as in the presence of adrenal tuberculosis or tumor metastases, or in cortical atrophy due to previous prolonged cortisone therapy, or following the resection of a functioning tumor of the opposite gland.

Acute adrenal failure usually occurs within the first 48 hours after operation. The signs and symptoms consist chiefly of a sharp *rise in temperature, tachycardia, shock, oliguria,* and *mental confusion*. There has not been time for the plasma electrolyte levels to change, and the measurement of urinary corticosteroid excretion in the emergency is utterly impracticable, for any number of reasons.

The mechanism of the shock is not clear, but it has been suggested that cortical hor-

mones are required for the normal effectiveness of chemical substances which mediate vascular tone

Once adrenocortical insufficiency has been diagnosed, the treatment consists of giving adequate amounts of hydrocortisone intravenously and intramuscularly We give 100 mg. intravenously 4 times a day, over each 6-hour period ACTH may or may not be helpful it might be useful if failure were due to adrenocortical atrophy but not if failure were due to adrenal excision or destruction Even in atrophy the effect of ACTH might require several days to appear

Subacute adrenocortical failure When the presence of a modicum of remaining adrenocortical function cushions the onslaught of the physiologic reaction to cortical hormone withdrawal, permitting the patient to slide gradually into failure a picture develops which is much different from that of acute failure There has been time for substantial losses of sodium to occur and this is reflected in a lowered plasma sodium level and a rise in the NPN though the latter need not necessarily be due to sodium loss *per se* The patient becomes weak listless drowsy, and anorexic (Fig. 245) Previously alert, he cannot remain attentive, and he may not remember what has just been said. Fever is not a common finding at this stage and the decline in blood pressure is not as abrupt as in acute failure.

While much of the symptomatology may be palliated by the administration of saline solution and desoxycorticosterone acetate (DOCA) a glucocorticoid such as hydrocortisone is usually also required to support metabolic processes other than those involved in fluid metabolism. We usually give hydrocortisone salt solution and frequently, ACTH to stimulate the remaining adrenal tissue This treatment is continued until general health and plasma electrolyte values are normal after which it is gradually reduced to a maintenance level or discontinued.

At times hydrocortisone may not prove completely adequate as a replacement sub-

RMcD Cushing's Syndrome (mild)
Excision Left Adrenocortical Adenoma

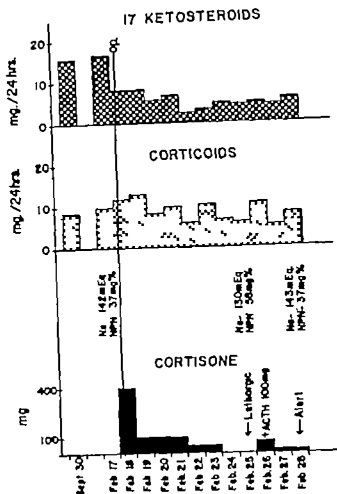


Fig 245 Case study subacute adrenocortical failure (From HARDY J D *Fluid Therapy* Philadelphia Lea & Febiger 1954) This middle-aged lady had had a benign left adrenocortical adenoma excised by thoracoabdominal approach on February 18 On February 25 her daughter who was a registered nurse noted that the mother was disoriented and unable to remember conversation from one moment to the next. Cortisone had been reduced from the 400 mg. given during the first 24 hours following operation to 100 mg. on each of the next 3 days, then to 50 mg. for 2 days, and then stopped Thus, when she became lethargic on February 25 she had had no steroid replacement therapy for almost 48 hours. Plasma sodium and blood nonprotein nitrogen (NPN) levels were obtained at once and were 130 mEq per L., and 58 mg per 100 cc respectively Cortisone and adrenocorticotropic hormone (ACTH) promptly restored the mental state and the blood chemistry levels to normal. This patient had the electrolyte abnormalities of subacute failure here findings were in sharp contrast to the findings met in sudden or acute failure—high fever rapid pulse hypotension, and apprehension followed by disorientation and coma.

stance and the addition of DOCA (or, soon, aldosterone?) may be required

Chronic adrenocortical failure This syndrome is well known Asthenia, marked weight loss, hypoglycemia, salt loss, and skin pigmentation are prominent features

Tetany during corticosteroid therapy Large doses of corticosteroid therapy may produce "hypocalcemic" tetany This is apparently due more to the mild alkalosis which occurs than to an absolute reduction in the total serum calcium level It was pointed out earlier (p 68) that normal neuromuscular irritability is dependent largely upon the ionized calcium fraction, which is diminished by alkalinization

Complications of Adrenocortical Therapy for Conditions Other Than Adrenal Insufficiency

Most of the more important considerations in adrenocortical hormonal therapy for adrenal insufficiency have been touched upon However, it remains to note that undesirable or even harmful effects may attend intensive or prolonged steroid therapy These have been presented in Figure 246 It may be seen that, with the particular exception of cortical atrophy, most of the side effects or sequelae are due to exaggeration of usual adrenocortical effects Hence, the "toxicity" lies more in the direction of excessive dosage, or in derangement of normal endocrine balance, than it does in any toxic effect *per se*

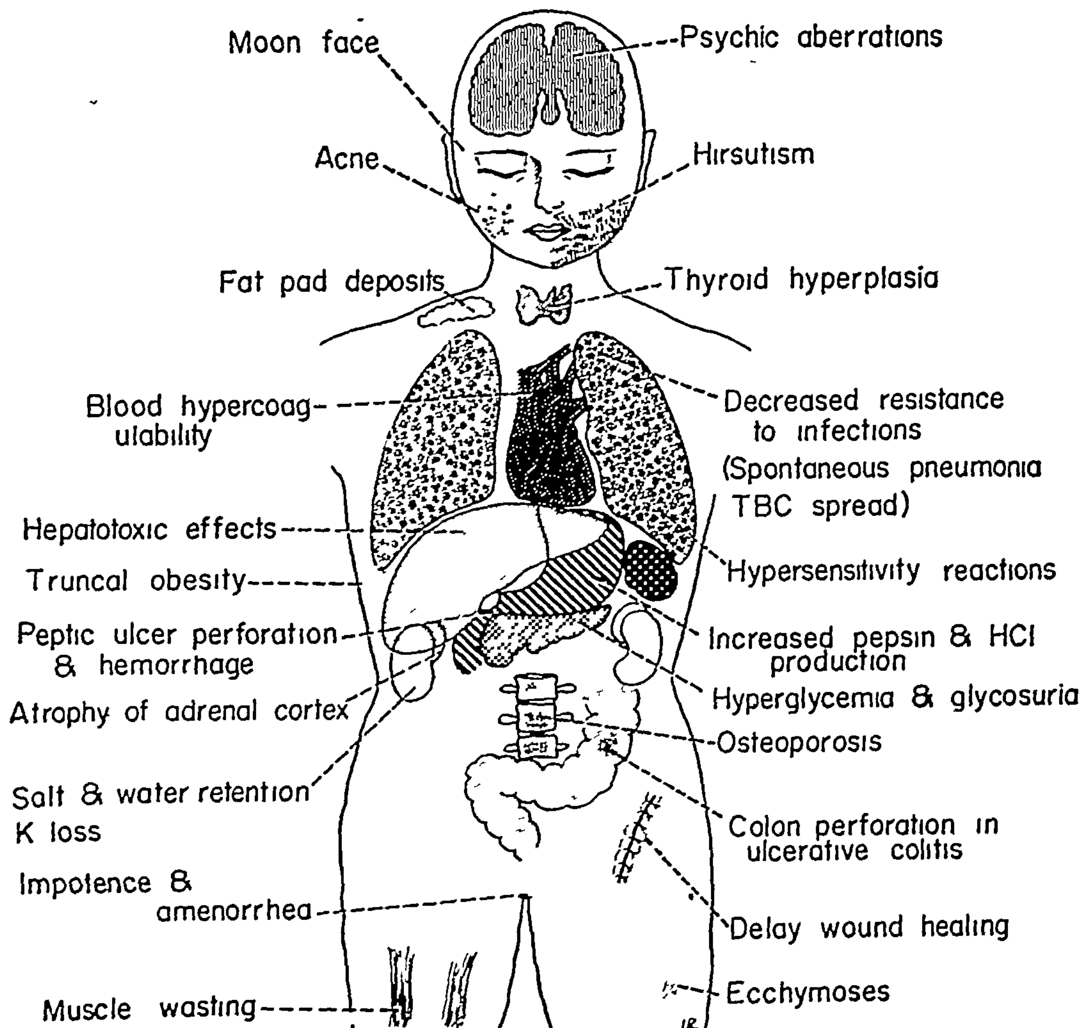


Fig 246 Side effects of corticosteroid therapy usually represent excessive manifestations of normal potentialities (From Hardy, J D, and Meena, A L Hazards and safeguards in steroid therapy Surg Clin North America, October, 1957: 1425)

n concluding this comment, one might nt out that (1) adrenocortical hormones not act specifically against any particular case, and inflammatory reactions caused many different agents may be radically dified by these drugs, (2) bacterial or nisms and their toxins are not directly tralized by these compounds, for in lobar eumonia their administration may abolish patient's symptoms while permitting the eumococci to continue to multiply in the od stream, (3) the effect of these hor nes is largely suppressive and whereas ring treatment they may modify tissue iction to various noxious agents, manifes- ions of the disease frequently return when drugs are stopped At times it is neces y to begin ACTH therapy before one can p prolonged hydrocortisone treatment is is because adrenocortical atrophy and uitary hypofunction have occurred In ct it may be quite difficult to "wean" the tient from chronic adrenal steroid ther y One should follow plasma sodium and PN levels for several days before relaxing se observation of such an individual

The Adrenal Medulla

The only known function of the adrenal edulla is to secrete epinephrine and nor inephrine, though other substances may identified in the future The tumor of the renal medulla is called a pheochromocy ma but not all of these neoplasms secrete cessive amounts of sympathomimetic sub- ances To our knowledge, hyperplasia com arable to that which involves the adrenal rtex, as a cause of adrenal medullary ypersecretion has not been reported The drenal medulla is not essential to life nd this is readily demonstrated by the dequacy of cortical replacement therapy llowing total adrenalectomy

heochromocytoma

HISTORICAL ASPECTS This tumor was de- cribed by Manasse[74] as early as 1893, but was not until 1922 that Labbé Tinel and Doumer[44] recorded the first complete study f a classic case. Their patient was a young woman who suffered severe attacks of vomiting associated with tremor, chilliness, and palpitation The blood pressure was usually elevated but was highly variable When the patient died in acute pulmonary edema, autopsy revealed a pheochromocytoma above the left adrenal gland Four years later Vaquez, Donzelot, and Gerandel[101] reported the first case of paroxysmal hypertension diagnosed during life This patient was treated with deep roentgen therapy over both adrenals and a remission was achieved. The first patient surgically explored and thereby cured was a woman who had attacks of paroxysmal hypertension associated with dyspnea, headache, tachycardia and vomiting, C H Mayo successfully removed a tumor intimately associated with the left adrenal gland.[76] Finally, in 1937 Beer, King, and Prinzmetal[16] demonstrated preoperatively in an animal preparation a pressor substance in the patient's blood during hy pertensive crisis, an effect which was ab sent following surgery

PATHOLOGY OF PHEOCHROMOCYTOMAS This tumor is formed by chromaffin cells which are derived from the neuroectoderm of the neural crest, and which are developmentally related to the cells of the sympathetic ganglia These lesions may be benign or, rarely, malignant However, to demonstrate malig nancy the tumor must have metastasized for, microscopically, benign tumors are in distinguishable from malignant ones Moreover even though most tumors are microscopically benign, if they secrete excessive amounts of epinephrine-like substances they are physiologically malignant, for they will eventually cause the death of the patient.

Usually small, round, encapsulated and unilateral, these tumors were found bilaterally in 16 of 152 cases reported by Mac Keith.[73] Furthermore while they are usually found in the adrenal glands or nearby, they may be situated elsewhere in the abdomen and even in the thorax Whereas the normal adrenal medulla contains only about 0 4 mg. of epinephrine per gm. of tissue assays of pheochromocytoma tissue have resulted in values which varied from 0 12 to 20 mg per

gm of tumor tissue Goldenberg and his associates[49] used paper chromatography to demonstrate the presence of norepinephrine in the adrenal medulla, and it was subsequently demonstrated that the functioning pheochromocytoma secretes both epinephrine and norepinephrine In recent years it has become possible to measure the blood levels of these catechol amines

Pheochromocytoma and neurofibromatosis One relationship of particular interest is that pheochromocytoma is related to certain neurocutaneous syndromes, and approximately 5 to 10 per cent of cases are associated with von Recklinghausen's disease Thus, stigmata of neurocutaneous disease such as *café-au-lait* spots or nodules in a hypertensive patient should arouse the suspicion of pheochromocytoma

Pheochromocytomas are surely more common than was formerly realized, and the intense interest in essential hypertension now results in more frequent detection of these tumors All cases of essential hypertension should be screened with a Regitine test (see below)

DIAGNOSIS OF PHEOCHROMOCYTOMA *Signs and symptoms* The paroxysmal attack or "crisis" frequently associated with pheochromocytoma is the result of the intermittent liberation of excessive amounts of epinephrine and norepinephrine into the blood stream The history may date back for years and initially the disease may have been mild As the months and years pass, though, the episodes are apt to increase in severity Approximately one-half of the patients have spontaneous attacks, but others are aware of precipitating factors such as postural changes, emotional or physical stress, pain, constipation, and menstruation In the full-blown attack the symptoms experienced are palpitation, precordial distress, nausea, vomiting, dizziness, circumoral pallor, coldness of the extremities, glycosuria, headache, and anxiety Dilatation of the pupils may be noted, and pulmonary edema may be sufficiently severe to cause death The attacks may last from a few minutes to several days, though ordinarily the episode is terminated within from one to two hours Initially the blood pressure usually falls to normal levels between paroxysms, but eventually it may become chronically elevated, rendering differentiation from essential hypertension difficult

The *modes of death* in cases of untreated pheochromocytoma are acute pulmonary edema with shock and collapse during the crisis, cerebral hemorrhage, or chronic renal or cardiac failure

Hypermetabolism and an increased basal metabolic rate are the result of an increased secretion of the medullary hormones and often lead to the erroneous diagnosis of hyperthyroidism Indeed, such patients have been subjected to thyroidectomy In addition, the excess epinephrine may produce the picture of "diabetes mellitus," which clears on resection of the tumor It has been suggested that this is, in effect, "steroid diabetes" from ACTH release, but it may be epinephrine-induced glycogenolysis In any event, when "diabetes," hypertension, and hypermetabolism are found in the same patient, pheochromocytoma should be seriously considered

In at least two patients of whom we have first-hand knowledge, *gastroduodenal hemorrhage* was the presenting manifestation of pheochromocytoma

Physical examination may reveal an *abdominal mass* in the flank If on massage of the mass a typical attack is induced, the diagnosis of pheochromocytoma is virtually certain If a tumor is not palpable, massage of the abdominal wall may still precipitate an attack, though the tumor is not necessarily present on the side massaged

Roentgenologic measures should be directed toward visualization of the kidney areas and the chest These have been discussed elsewhere under the diagnosis of adrenocortical tumors However, again, the tumor need not lie adjacent to the kidney Aortography has been reported to assist in the diagnosis of the lesion, but we have not tried it

Additional laboratory studies and clinical tests As indicated above, the fasting blood sugar level may be elevated as a result of the excessive secretion of epinephrine In addition, there may be a decreased glucose tolerance suggestive of diabetes mellitus, though more commonly the glucose tolerance curve is normal Glycosuria may be found. The basal metabolic rate may be increased, and the urinary excretion of corticoids is elevated in the occasional case, apparently because of ACTH release During an attack the plasma epinephrine and norepinephrine levels may be measurably increased, as previously mentioned

Specific diagnostic chemical tests In 1933 Fourneau and Bovet[49] published their work on the use of benzodioxane compounds as "*sympathicolytique*" agents, and since that time a number of these compounds in addition to other chemical agents, have been used as tests and as treatments in cases of pheochromocytoma The more important of these will now be outlined briefly

Provocative tests The histamine test — The purpose of this test is to attempt to precipitate the usual hypertensive crisis in a patient suspected of having a pheochromocytoma but whose blood pressure is normal at the time the patient is seen The usual procedure is to administer 0 05 mg. of histamine base intravenously In normal subjects hyperreactors, and patients with essential hypertension the reaction is approximately equivalent to the blood pressure rise which results from the cold pressor test and the patients with essential hypertension may show some circumoral pallor and may have headache In the patient with pheochromocytoma however an attack may be precipitated within 2 minutes, consisting of severe headache distress and pain in the abdomen and later in the chest groaning, restlessness anxiety more circumoral pallor, and excessive sweating associated with a marked rise in blood pressure

While this test is useful, it may fail to produce an attack in the patient who actually does have a functioning pheochromocytoma.

The mecholyl test —This test also is used to attempt to precipitate a crisis in a patient whose blood pressure is normal at the time of examination Twenty five milligrams of this drug are given subcutaneously An initial blood pressure fall of short duration, followed by a marked and more sustained rise to hypertensive levels, constitutes a positive test False positives with the test are said to be few, but a failure of response does not rule out the presence of pheochromocytoma.

Adrenolytic agents Whereas the provocative agents are used to attempt to precipitate an attack and achieve a positive diagnosis in the patient in whom pheochromocytoma is suspected but whose blood pressure is normal at the time of examination, the adrenolytic agents are used to attempt to lower the blood pressure in patients who have hypertension when examined. It is assumed, though not entirely correctly, that the blood pressure of the patient with essential hypertension will not be lowered by the administration of these drugs, while in the patient whose hypertension is due to medullary hormones the blood pressure will fall

Piperoxan (benzodioxane) and Dibenamine —Piperoxan was one of the first of these agents to be used for the diagnosis of pheochromocytoma This agent was of value and frequently accurately indicated the presence of a pheochromocytoma Nevertheless, it occasionally gave false negative as well as false positive results. That is, it failed to lower the hypertensive blood pressure in some patients with pheochromocytoma, and in some patients in whom it did lower the blood pressure no pheochromocytoma was found. It is now little used

Dibenamine —This drug does block the effect of circulating epinephrine and norepinephrine, and it will cause a drop in blood pressure when a pheochromocytoma is elaborating these substances. Yet it also may depress the blood pressure in the presence

of essential hypertension and this feature is of course a serious defect in the test

Regitine (C-7337).—This substance was first used by Grimson and his associates,[51] and it has since been widely used in the detection of pheochromocytomas. They used 5 mg. doses intramuscularly, and found fewer side effects than with benzodioxane. A single intramuscular injection of 5 mg. of Regitine may be considered adequate for routine tests in hypertensive patients to detect circulating epinephrine elaborated by a pheochromocytoma. Piperoxan can be used as a confirmatory test.

Subsequent experience by others confirmed the fact that Regitine offered a more useful test in the diagnosis of pheochromocytoma than did piperoxan. According to Gifford, Roth, and Kvale,[47] Regitine is most reliable when given intravenously (in doses of 5 mg.). Regitine produced a marked fall in blood pressure in patients with sustained hypertension secondary to pheochromocytoma and, while it did have some depressor effect on blood pressure in 66 per cent of patients who had essential hypertension, the blood pressure of the patients was usually decreased less than 35 mm. Hg systolic and 25 mm. diastolic. False positive reactions were obtained in 3 out of 149 patients without pheochromocytomas to whom Regitine was given intramuscularly and in 4 out of 107 patients to whom Regitine was given intravenously. These false positive reactions were attributed to the following factors: (1) sedation before the test, (2) uremia, (3) basal blood pressures that were in the low hypertensive range, and (4) the unexplained depressor effect of Regitine on the blood pressure of some hypertensive patients.

The effect of adrenolytic drugs on pheochromocytoma with functioning metastatic lesions.—In a particularly exacting test of the efficacy of the various drugs which are available for the treatment of hyperepinephrinemia, Bannon and Allen[9] studied the efficacy of piperoxan, Regitine, Priscoline, Dibenamine, and Dibenzyline in a patient with functioning metastases from a pheochromocytoma. The problem presented *preoperatively* by the patient was that of how to reduce the blood pressure in order to improve the general condition of the patient sufficiently so that operation could be performed without too great a risk. The problem *postoperatively* was that of how to reduce the blood pressure which was high because of the functioning metastases. It was found that although piperoxan (benzodioxane) produced a moderate reduction in blood pressure on continuous intravenous or intramuscular administration, refractoriness to its adrenolytic action developed. Moreover, the duration of its action was so short as to render it of little use in sustained therapy. Large amounts of Regitine were used, but refractoriness developed to its action also. The effect of Priscoline was dramatic, but its brief action precluded sustained therapeutic use. Dibenamine reduced the blood pressure in a satisfactory manner, but the duration of its action was brief. Finally, the intravenous and oral administration of Dibenzyline, a relative of Dibenamine, proved to be effective in counteracting the symptoms and signs of hyperepinephrinemia for a prolonged period. During the 7 months of administration of this drug, no toxicity was noted and refractoriness did not develop. Its use allowed adequate preparation of the patient for operation and successful treatment of the postoperative recurrence of hypertension.

MANAGEMENT OF PHEOCHROMOCYTOMA. Having diagnosed the presence of a pheochromocytoma by history, by such findings as physical examination may reveal, and by the appropriate tests, the definitive treatment consists of excision of the tumor. Occasionally physical examination or roentgen studies may have disclosed the location of the tumor, but often it is not possible to lateralize it preoperatively. If the side involved can be determined prior to operation, a relatively short thoraco-abdominal incision is preferred; otherwise a short transverse upper abdominal incision is made, through which the adrenal areas are ex-

plored The incision may then be extended in either direction. Recall that from 10 to 15 per cent are bilateral

A good *basal anesthetic* is helpful in avoiding emotional reactions which may precipitate an attack preoperatively, and a general anesthetic is desirable Contrary to the situation with a functioning adrenocortical tumor, the adrenal medulla opposite the one giving rise to a pheochromocytoma does not undergo atrophy, though no ill effects would occur if it did.

It is desirable to expose the tumor and to ligate the blood supply as early as possible, since manipulation of the tumor may liberate large amounts of epinephrine with resulting excessive blood pressure levels As a further precautionary measure, an intravenous drip of Dibenamine or Regitine should be available to use during the operation in the event that manipulation of the tumor produces excessive blood pressure levels In fact some surgeons continue a slow drip of an adrenolytic drug throughout operation as a prophylactic measure

Postresection shock One much disputed circumstance which not infrequently follows resection of a pheochromocytoma is that profound shock may occur shortly after the tumor has been excised. The etiology of this hypotension is not clear Bartels and Cattell[13] stated that this type of collapse may occur while the pheochromocytoma is still *in situ* If so, it would seem that an excess of epinephrine rather than a lack of it is the cause of the shock, and that the circulatory collapse is due to acute failure of the left side of the heart This view is further supported by the report of Grimson and his coworkers[31] on the beneficial effect of benzodioxane when used continuously throughout the operation to neutralize excessive amounts of circulating epinephrine In stark contrast others maintain that it is a lack of epinephrine which is causing the shock, and evidence has been advanced to support this view also In a patient operated upon by Decker McDowell, and Trimble[20] manipulation of the tumor caused the blood pressure to spike to 280/180 The tumor had two or three vascular pedicles, which were clamped and ligated The mass was shelled out easily, leaving some yellowish, normal looking adrenal gland behind As one vessel was being clamped, the blood pressure suddenly dropped to 60/20 and an intravenous injection of solution containing 5 mg. of epinephrine and 500 cc of isotonic sodium chloride solution was started immediately The pressure was well controlled by this method and was maintained at about 100/60 The patient received 500 cc of blood during the operation During the first night after operation, however, the needle used for the intravenous injection of the epinephrine solution became plugged and before the solution could be started again the blood pressure dropped to 40/10 In the haste of starting the epinephrine solution again, too much was allowed to enter the vein and the pressure suddenly rose to 200/100 and the patient developed a severe headache. The drip was regulated immediately and the patient had no further trouble Epinephrine solution was used at intervals during the next 3 days, and the systolic blood pressure was maintained by this means at between 90 to 140 mm. Hg. However the picture in their subject was somewhat confused by the fact that during the early postoperative period the patient was transfused because of a low hemoglobin level

Further suggestive data in favor of the epinephrine deficiency theory were offered by Litman and State[76] who reported a fatality in the case of an 11 year old girl who received Dibenamine preoperatively and then went into profound irreversible shock immediately after the removal of a pheochromocytoma. She was given large doses of epinephrine but without effect, and it was believed that the Dibenamine had rendered the patient refractory to epinephrine

Clearly, the question of the cause of this interesting shock phenomenon remains unsettled Fortunately, it is not usually a severe problem, and with judicious medication hypertension caused by manipulation of the

tumor, and hypotension following its removal, can be controlled If the hypertension has not become fixed because of the chronic presence of the pheochromocytoma, the prognosis following resection of the tumor is excellent

THE HAZARD PRESENTED BY INCIDENTAL PHEOCHROMOCYTOMA AT OPERATION It is highly dangerous to perform, say, a cholecystectomy on a patient who has a functioning pheochromocytoma, the subject may die in hypertensive crisis Of 15 cases of pheochromocytoma diagnosed at autopsy, Minno, Bennett, and Kvale[83] noted that 5 had died during operation for other lesions

Endocrine Disorders of the Pancreas

Hyperinsulinism

HISTORICAL CONSIDERATIONS Possibly the first time that the pancreas was associated with diabetes and glucose metabolism was in 1788, when Cawley[27] reported the autopsy findings of a diabetic patient who presented pancreatic calculi In 1856 Claude Bernard[18] wrote upon glycosuria and hyperglycemia with a perception which considerably clarified and advanced knowledge in this field In 1869 Paul Langerhans[67] described the islands to which his name was subsequently affixed In 1884 Arnozan and Vaillard[3] ligated the ducts of the pancreas and noted an atrophy of the acinar tissue and a persistence of the islet cells They failed, however, to attach significance to the persistence of the islet cells in an animal which did not develop diabetes A fatal diabetes in animals was produced by pancreatectomy in 1889 by von Mehring and Minkowski[80] and in 1891 Minkowski[82] demonstrated that a successful graft of pancreatic tissue would prevent diabetes following total pancreatectomy, with diabetes ensuing when the graft was also excised A further step in the eventual solution of this problem was taken when Schafer,[94] in 1895, noted the evidence favoring an internal secretion of the pancreas, he pointed out that, while total pancreatectomy produced a fatal diabetes, a total external pancreatic fistula did not In 1901 Opie[87] described hyaline changes in the islet of diabetics at autopsy, and in 1922 Ba and Best[10] isolated insulin and demonst its potency in the treatment of diabetes litus

Shortly following the discovery of in Seale Harris[56] observed that symptor hypoglycemia similar to those of in shock occurred in certain patients spontaneous hypoglycemia, and sugg that this could be due to hyperplasia or plasia of the isles of Langerhans T years later such a case was studied by sell Wilder and his staff,[106] and this pa a physician suffering from a syndrome gestive of insulin shock, was operated by W J Mayo A tumor of the pan was found (with multiple liver metast which represented an islet cell carcin biologic assay on standardized rabbit vealed that the metastases containe sulin, as shown by their ability to l the blood sugar in these animals The case successfully treated surgically wa erated upon by Roscoe Graham of To and was reported by Howland and his ciates [61] At operation a benign adenon islet tissue was removed and the patient cured

PATHOLOGY OF ISLET CELL TUMORS No islet cell tumors secrete increased amoun insulin They may be found as incid findings at autopsy One obscure typ islet cell tumor described by Zollinger Ellison[109] has been termed the "ulcerog tumor of the pancreas", it may be assoc with a particularly virulent type of pe ulceration due to greatly increased acid cretion This ulcerogenic tumor may be, more often is not, linked with the secre of increased amounts of insulin It usu is derived from alpha cells or delta cell

The tumors of the isles of Langerhans usually reddish brown in color and cont with the yellow or ivory color of the rounding pancreas Moreover, the neopla are of a firmer consistency than surrounc tissue They are typically benign, well cumscribed, and average from 1 to 2 cm

diameter They are found more frequently in the tail or body of the pancreas, since islet tissue is more abundant in these areas Nevertheless, this is only a relative matter, since of 76 patients reviewed recently from the experience at the Mayo Clinic 19 had tumors of the head, 22 of the body, and 28 of the tail of the pancreas. The other tumors were at the junction of the body and tail, or were multiple, and in one case the location of the tumor was not stated[22] The fact is one must search carefully for nodules in the head of the pancreas and in all other sites. Since the tumors can be multiple, many patients with islet cell adenomas have had at least one previous operation at which a tumor may or may not have been found More often, of course, these adenomas are solitary The size of the lesion bears little relationship to the severity of the disease, that is to the amount of insulin secreted and to symptoms

Does islet cell hyperplasia occur? While it may be true that very rarely the hyper insulinism is due to generalized hyperplasia of the islet cells the frequency with which this is diagnosed tends in all reported studies to be inversely proportional to the care with which the surgeon seeks for the adenoma at the time of operation Moreover, the adenoma has often been found in pancreatic tissue that was resected because no tumor could be discovered. Furthermore, the tumor has at times been found at autopsy in patients in whom a part of the pancreas had been resected but the hyperinsulinism had not been satisfactorily managed Thus one must be exceedingly cautious in diagnosing the hyperinsulinism as being the result of generalized islet cell hyperplasia lest the small adenoma be overlooked In 76 of 94 cases reported from the Mayo Clinic, an actual tumor of the islet cells of the pancreas was found, therefore Breidahl, Priestley, and Rynearson[22] believe that if hyperinsulinism due to diffuse hyperplasia of the islet cells does exist it must be exceedingly rare they have found no patient in whom this condition was definitely established by pathologic examination

The majority of islet cell adenomas are benign In the Mayo Clinic experience there were 46 benign adenomas, 23 Grade I carcinomas, and 7 metastasizing carcinomas of the isles of Langerhans

Hyperinsulinism may be encountered from childhood to late adult life, though the greatest incidence is in the fourth, fifth, and sixth decades.

THE DIAGNOSIS OF HYPERINSULINISM. The diagnosis of hyperinsulinism rests upon the hypoglycemia produced and the symptoms which ensue therefrom Causes of hypoglycemia include organic hyperinsulinism (islet cell adenoma), functional hyperinsulinism, the hypoglycemia of liver failure, and the hypoglycemia of pituitary or adrenal failure

The organic causes in which a recognizable anatomic lesion can be found, are hyperinsulinism due to pancreatic islet cell adenoma or carcinoma, hepatic disease, pituitary hypofunction, adrenocortical hypofunction, and certain central nervous system lesions There are, in addition, functional states of hyperinsulinism in which no recognizable anatomic lesion has been demonstrated but which are probably due to a relative hyperinsulinism. Finally, there are the other causes such as factitious hyperinsulinism which is occasionally encountered in persons of questionable sanity or in malingerers.

Signs and symptoms of hypoglycemia Wilder[104] grouped the *nervous components* of this syndrome under three headings (1) those related to the vegetative nervous system, consisting of nausea, sweating, pallor, flushing chilliness and syncope, (2) those arising from the central nervous system, represented by restlessness tonic or clonic muscle spasm opisthotonous and convulsions and (3) psychic disturbances such as apprehension disorientation, mania confusion unconsciousness and coma. Abdominal pain may be prominent

Whipple's triad embodies findings which establish the diagnosis In 1947 Whipple[104]

re-emphasized the following findings which have now been recognized as representing an almost indispensable diagnostic grouping first, the "attacks" come on characteristically in the early morning during the fasting period before breakfast, or following intensive mental or physical effort when sugar reserves are low, second, during the attacks or after a prolonged fast of at least 24 hours the blood sugar levels are below 50 mg per 100 cc , third, the patients recover promptly from the "spells," whatever their pattern may be, on administration of sugar by vein or by mouth

When this triad has been rigidly sought and demanded, there has resulted a gratifyingly high percentage of accurate preoperative diagnoses Whipple found a tumor in 27 of 32 cases in which a typical triad was present preoperatively

The *relation of consciousness to the blood sugar level* is of interest There is not a particularly good correlation between the blood sugar level and the state of consciousness, though in general a very low blood sugar level (less than 30 mg per 100 cc) will be associated with mental confusion and possibly coma

The symptoms may occur slowly or suddenly, and may or may not be associated with loss of consciousness Briedahl and his associates[22] pointed out that the pattern of symptomatology is usually constant for any one individual, although the severity of symptoms may vary with different attacks They considered it likely that some tumors secrete insulin constantly, as would be expected, and, if so, the attacks occur at the same time every day Other tumors, on the contrary, appear to have intermittent secretion, paroxysmal attacks occurring at irregular and infrequent intervals

Repeated, severe attacks with unconsciousness may be associated with temporary or even permanent neurologic changes, and a progressive mental deterioration may be seen in longstanding cases For this reason the treatment of suspected cases should be delayed no longer than is necessary to establish the diagnosis

Difficulty in diagnosis If the possibility of hyperinsulinism is kept in mind, the low blood sugar level will suggest the presence of this state of hormonal imbalance and the possible conditions with which the diagnosis of islet cell adenoma may be confused will readily be eliminated by a few appropriate studies Yet, there often is considerable delay before the correct diagnosis is arrived at Among the patients reported by Breidahl, Priestley, and Rynearson,[22] 14 had been diagnosed as having epilepsy, 2 as having tetany, 6 as psychosis, 4 as hysteria, 3 as menopause, 2 as brain tumor, 2 as diabetes, 2 as being drunk, and 1 as a heart attack—all before the correct diagnosis was made With refreshing candor, Breidahl and his associates noted that the initial diagnosis of chronic nervous exhaustion in 2 patients was made at the Clinic, though later the true nature of the illness in these patients was appreciated and the hyperinsulinism treated

MEDICAL MANAGEMENT The chief disadvantage of delaying treatment, once the diagnosis is made, is that repeated attacks may produce permanent neurologic or mental damage The use of medical therapy, consisting of frequent feedings every few hours, is likely to produce a markedly obese individual, and this therapy is thus not feasible in most instances

The use of corticosteroid therapy in the management of hyperinsulinism The diabetogenic effect of cortisone and hydrocortisone has led to the use of these compounds in the management of the hypoglycemia of hyperinsulinism Cortisone effectively controlled the hypoglycemia of an islet cell adenoma and hydrocortisone was later found to afford similar results More recently, glucagon has been used in the management of states of hyperinsulinism Secreted by cells of the Islets of Langerhans, this substance promotes glucose utilization and thus functions as an insulin antagonist

In studying the effect of hydrocortisone in acute hypoglycemia, Frawley[46] noted that pyruvic acid concentrations in the blood might be significantly increased without marked changes in glucose or fructose The changes in pyruvic acid, potassium, and phosphorus metabolism which characterize and distinguish steroid diabetes from diabetes mellitus were emphasized

SURGICAL MANAGEMENT A transverse upper abdominal incision is a suitable one. Need less to say, the search for the adenoma must be orderly and painstaking.

Preoperative and postoperative care Preoperatively the patient should come to the operation with an intravenous glucose drip running to avoid hypoglycemia during operation. Postoperatively the subject may manifest a moderate hypoglycemia which need cause little concern, though the development of frank diabetic acidosis should be prevented with appropriate insulin dosage. Fortunately, the normal islet cells do not usually manifest the same degree of atrophy in the presence of a functioning adenoma as do the parathyroid glands or the adrenal cortex opposite the one containing a functioning tumor Though the patient may present a mildly diabetic picture in the immediate postoperative period this is usually of little moment.

Prognosis The results are excellent when the adenoma is found and removed provided irreversible cerebral changes have not occurred as the result of chronic disease and repeated attacks of hypoglycemia. The results are far less satisfactory when no adenoma is found and a subtotal or total resection of the pancreas is resorted to—for usually the adenoma has been overlooked Total pancreatectomy is a somewhat formidable procedure and deprives the patient of normal physiologic processes of digestion. In addition there are serious complications which often follow resection of this organ

Hypoinsulinism (Diabetes Mellitus)

Diabetes mellitus results from inadequate amounts of circulating insulin Methods for the measurement of insulin content of blood are not precise, but a method utilizing the effect of insulin on the glucose utilization of the isolated diaphragm was reported by Groen and associates[52] Prior to this method, the probable insulin content of blood was estimated by noting the hypoglycemic effect of serum from the patient on the blood sugar level of especially prepared rabbits.

It is not desirable to present here a detailed review of the pathophysiology of diabetes mellitus Basically, an inability to utilize glucose to satisfy energy requirements results in the combustion of fat, which is inefficiently metabolized The overproduction of acid ketone bodies depletes the total base, with resulting dehydration (as base is not available to hold water)

Recent contributions to the understanding of experimental diabetes have been reviewed by Stetten[90] The impairment in glucose utilization is widespread and includes the several normal fates of glucose, such as glycogenesis fatty acid synthesis, pyruvic and lactic acid formation, and the total oxidation of glucose to carbon dioxide

DIAGNOSIS OF DIABETIC ACIDOSIS IN SURGICAL PATIENTS A history of weight loss, polyphagia, polydipsia, and polyuria should certainly suggest the possibility of diabetes mellitus The disease should also be considered in any patient with severe or repeated infections especially of the toes

The duration and the severity of the metabolic disturbances, the resulting deficiencies and the extent of the therapeutic difficulties that may be encountered will often be suggested by a few preliminary exploratory observations and examinations The laboratory studies will reveal an elevated blood sugar level and glucose acetone, and diacetic acid will be found in the urine The initial blood sugar level does not necessarily indicate the degree of acidosis or the seriousness of the patient's condition since certain patients with extremely high blood sugar levels may require relatively little insulin to effect recovery from acidosis, while others

with a lower blood sugar level may require tremendous amounts of insulin

Acidosis is not rendered certain by the finding of a low plasma carbon dioxide combining power, since a lowered level is also found in compensated respiratory alkalosis Nevertheless, one will seldom be mistaken in diagnosing acidosis on the basis of a reduced carbon dioxide combining power when this finding is accompanied by clinical and other evidence of uncontrolled diabetes

TREATMENT OF DIABETIC ACIDOSIS IN SURGICAL PATIENTS The treatment of diabetic acidosis in the surgical patient will often consist both of the treatment of the diabetic acidosis *per se* and of the management of a precipitating or aggravating surgical condition such as a gangrenous extremity, or a carbuncle or other purulent collection Any condition which imposes an increased metabolic load upon the individual renders the diabetes more difficult to manage

The fluid problem is primarily one of insulin dosage and the restoration of body fluid and electrolyte balance Large deficits of sodium, chloride, potassium and, often, magnesium and phosphorus may exist In the treatment of severe acidosis or coma, Butler[23] recommends the administration of crystalline insulin in a dosage of at least 2 units per kg of body weight or 75 units per m^2 of body surface, given intramuscularly to avoid the possible delays of intravenous administration A similar amount of crystalline insulin is given intravenously with the first infusion He further recommends that at the beginning of therapy, with the first dose of crystalline insulin, a second injection of from 5 to 10 units of Protamine zinc insulin be administered, depending upon the age, size, and the past history of the patient—including past therapy, if this is known Thereafter the need for crystalline insulin is determined by frequent analyses of the urine sugar (preferably followed by means of an indwelling Foley catheter) and with such blood sugar measurements as may be considered necessary Several hundred units of regul[ar in]sulin may be required for the corre[ction] of diabetic acidosis in adults, and the [dos]age to be used is "enough" The s[erum] potassium level may be normal or ele[vated] on admission, but cellular stores of p[otas]sium will usually have been deplete[d. As] treatment progresses, potassium will us[ually] need to be administered This decline i[n] serum potassium level during thera[py is] further aggravated by the intracellular [dep]osition of potassium in the process of [gly]cogen formation following the admin[istra]tion of insulin

Blood transfusion and *antibiotics* are [given] liberally, and oral nutrition is begun as [soon] as feasible If balanced fluid prepara[tions] are available they should be used in [pref]erence to isotonic saline solution F[ortu]nately, such mixtures are now availab[le in] most hospitals, and additional amoun[ts of] potassium or, if desired, sodium chl[oride] can be added to these solutions We us[ually] employ sodium bicarbonate with its [dis]posable anion (HCO_3) to combat acid[osis,] though sodium lactate is satisfactory.

The Breast

The physiology of the breast is of [par]ticular importance to the surgeon in [re]spect to growth characteristics. Lacta[tion,] in contrast, raises surgical problems [only] when a galactocele or acute breast abs[cess] must be drained, or when breast carcin[oma] develops in a lactating breast

Functional Anatomy

CANCER SURGERY Certain aspects of br[east] structure (Fig 247) deserve commen[t in] connection with surgery for maligna[ncy]. The breast is, of course, a surface or exte[rnal] organ, since neither of the celomic cav[ities] is entered in the course of conventi[onal] "radical" mastectomy, the mortality [as]sociated with this operation is virtually [nil] if anesthesia is satisfactory and blood lo[ss is] replaced as it occurs

In approximately one-third of outer qu

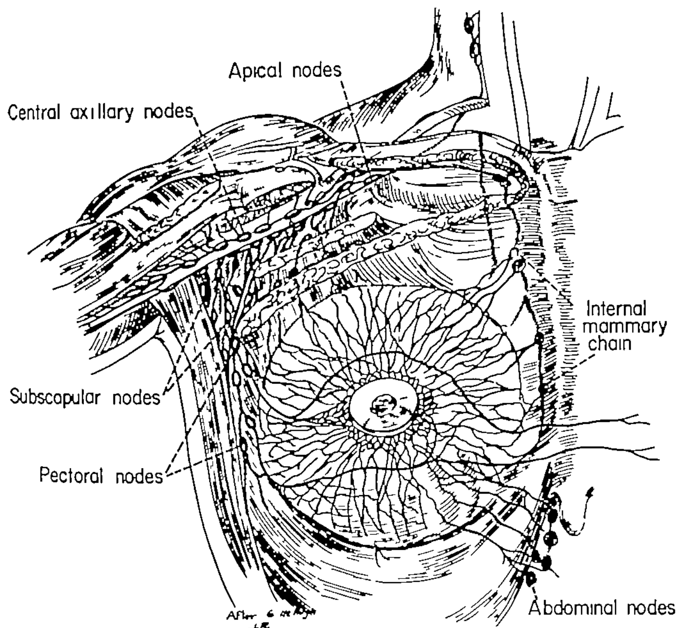


Fig 247 Hematogenous spread of breast cancer can occur independent of lymphatic channels.

rant cancers with axillary node metastases and in approximately two-thirds of inner quadrant cancers with axillary node metastases the internal mammary chain of nodes is involved. The fact that the incidence of internal mammary node involvement is increased in the presence of axillary node metastases may be due in part, to back pressure along the lymphatic channels due to blockage of the axillary lymphatics by tumor spread. Obviously the patient will not be cured by radical mastectomy if involved internal mammary nodes are not resected, and these are probably not often eradicated successfully

INTRADUCTAL PAPILLOMA. This tumor may or may not be a premalignant lesion. Like the problem of malignancy in gastric ulcer, it is a moot question whether the benign intraductal papilloma of the breast becomes malignant or whether the papilloma was malignant from its inception. While proof is difficult to marshal for either point of view to the exclusion of the other, I per-

sonally look upon an intraductal papilloma as a more serious lesion than the common extraductal fibroadenoma which occurs in young women and is usually the only bre tumor encountered below the age of 2(

The pertinent anatomic fact here, h ever, is that by massaging the breast the direction of the nipple when the m cannot actually be felt, one can often press blood from the ductal opening on surface of the nipple This permits idei fication of the pie-shaped segment of breast in which the offending papillom situated At surgery a probe can often passed into the involved duct (about ducts open upon the surface of the nippl Excision of the duct containing the pa loma can then be accomplished more p cisely, with less disfiguration of the bre If a probe cannot be passed into the d from which the serosanguinous fluid is pressed, then a short circumareolar cision overlying the duct will often per its identification as it extends to the nipp The bluish discoloration caused by int ductal hemorrhage is quite distinctive

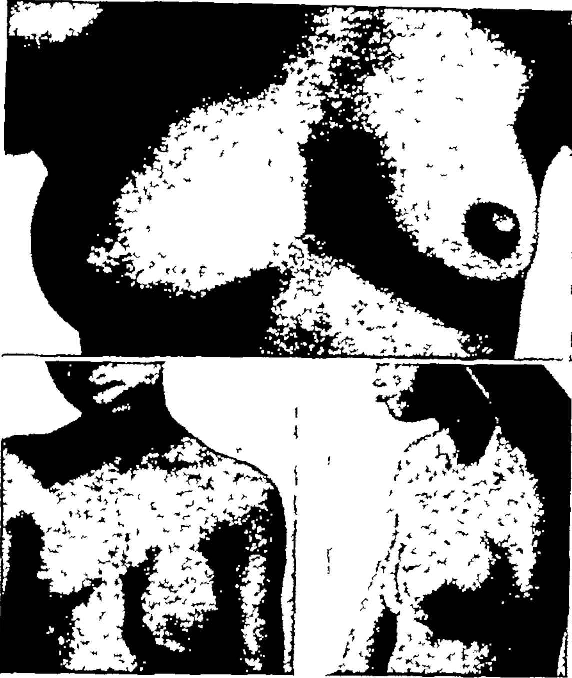


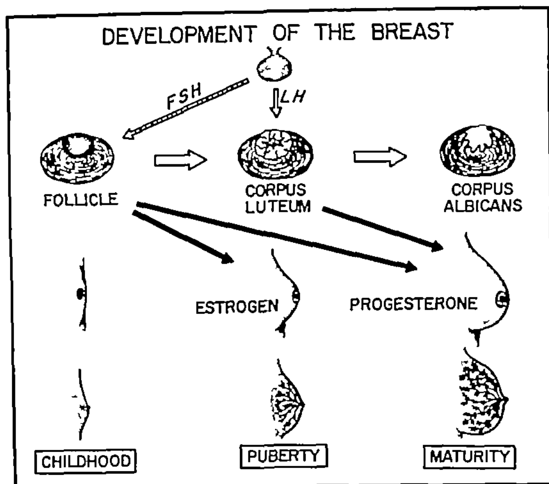
Fig 248 Above Virginal hypertrophy *Below* Rapidly growing fibroadenoma at puberty



Fig 249 Transient breast enlargement in boy at puberty Such temporary gynecomastia occurs more frequently than is generally realized When the balance swings definitely in favor of androgen secretion over estrogen secretion, the breast enlargement recedes in most patients In girls at puberty, one breast may begin to develop months before the other, thus, it is most important not to excise the "lump" with the thought that the mass beneath the nipple represents a tumor In time, one may assure the mother, the second breast will begin to develop Continued observation is desirable until this occurs

In general, one should use radial ratl than transverse incisions that sever un volved lactic ducts Yet, it has always be surprising to me how few complications a company transections of lactic ducts, e clusive of those in an actively lactati breast Full advantage should also be tak of the fact that incisions made just at t border of the pigmented areola (circur areolar incisions) heal with a scar that hardly visible This is of course desirab in women, but it is also desirable in m whose gynecomastia does not regress and excised The entire male breast (Fig 24 can be removed through a circumareol incision An obvious scar near the brea in a male will lead to questions which ma embarrass him

LOCAL ANESTHESIA The position and co figuration of the breast and its nerve suppl render local anesthesia particularly suitab for excision of benign masses and for sin ple mastectomy When there is little chanc that radical mastectomy will be neede local anesthesia is highly suitable for breas surgery in many patients



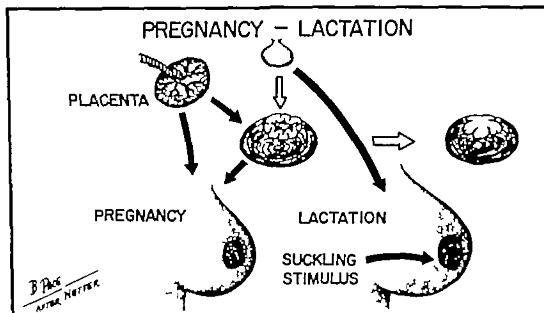


Fig 250 Endocrine factors in breast development and function. Most important are (1) follicle stimulating or gonadotropic hormone (FSH) which produces initial breast development through ovarian secretion of estrogens (2) progesterone from corpus luteum and later the placenta, which further prepares the breast for lactation and (3) pitocin from the posterior lobe of the pituitary which initiates lactation. The secretion of pitocin accounts for the familiar letdown reflex by which the mother exhibits a copious flow of milk, usually in response to neurogenic or psychic stimuli evoked by nursing of the young (After Netter F H. *The Ciba Collection of Medical Illustrations* Summit New Jersey Ciba Pharmaceutical Products, Inc 1948)

Hormonal Influences (Fig. 250)

ESTROGENS The secretion of estrogens promotes breast development, whether ovarian

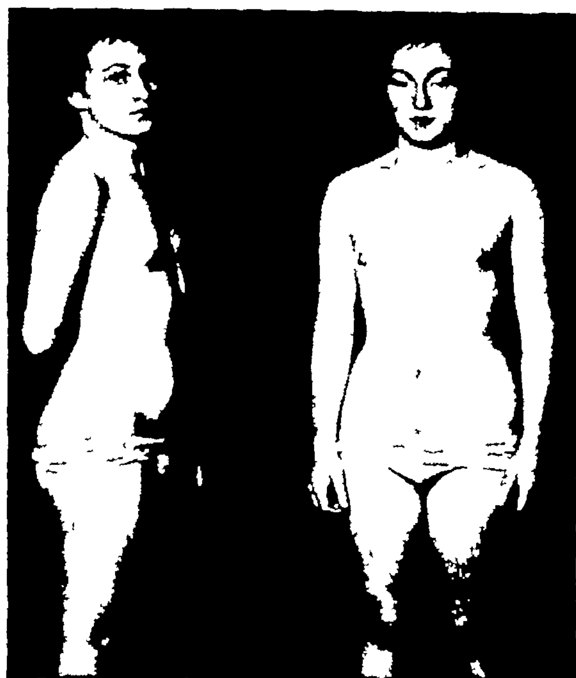


Fig 251 Breast development following adrenogenital syndrome This 14-year-old girl (Patient N C W, Figs 241 and 242) exhibits beginning breast development that was produced with oral cortisone therapy This treatment suppressed the pituitary secretion, with a consequent fall in androgen production Ovarian function stimulated by her gonadotropic hormones then brought about feminization, including a first menstrual period Note the short hair above the forehead, which was just beginning to grow again after the baldness produced by the adrenogenital syndrome



Fig 252 Gynecomastia due to malignant estrogen-secreting adrenocortical tumor

(Fig 248, 251) or adrenal (Fig 252 origin Under the powerful effect of ova estrogens stimulated by pituitary gon tropic hormones at puberty, the bre usually develop rapidly Yet, one br may begin to develop long before the o breast does, and the initial "lump" on developing side may be mistaken for a tu and, unhappily, excised If one tempo and reassures the parents, the second br will develop in time Of course, the n can represent a tumor, and close observa is indicated until the issue is settled T same problem arises in connection with usually transient breast enlargement male children at puberty

Virginal hypertrophy Breast devel ment may be excessive either unilater or bilaterally This "virginal hypertrop is usually a problem only when one br far outstrips the other (Fig 248) The larged breast may be truly enormous the difference is not great, nothing need done, for many women go through succ ful lives with unequal breasts Howe in some patients a plastic procedure (ma moplasty) is justifiable to reduce the gros disproportionate size of a huge breast

Gynecomastia Breast enlargement in male was alluded to above Unquestiona it is due primarily to estrogen stimulati though the mechanisms are not always cle Circumstances in which gynecomastia m be observed are (1) puberty (Fig 24 (2) estrogen therapy (as for prostatic ca cer), (3) cirrhosis (Fig 80), (4) starvati (5) functioning adrenocortical tumors (F 252), and (6) certain lung tumors

The explanation of breast enlargement connection with estrogen therapy or estrogen-secreting tumor is readily appare but the explanation in the instance of p berty, cirrhosis, or starvation is not so si ple In starvation and in cirrhosis it has be assumed that hepatic inactivation of andr gens was more effective than the hepa inactivation of estrogens Moreover, te ticular secretion of androgens doubtless diminished in these conditions, whereas t

adrenocortical secretion of estrogens may be relatively unchanged. Hence, the ever present hormonal balance, which decides whether the individual will have the male or the female secondary sex characteristics, swings in favor of female values. In male puberty, however, the explanation is still less clear Without question the estrogenic substances are largely responsible for the breast enlargement, which gradually subsides as androgens become preponderant. The subtle interplay of estrogens, androgens, and hepatic function at puberty requires much further study

ANDROGENS Male-type hormones suppress breast development in children (Fig. 251) or diminish breast size when the breasts are subjected to androgenic therapy during adult life That is, the estrogen androgen hormonal balance is shifted to the male side by androgen therapy or by adrenocortical hyperfunction that produces the adrenogenital syndrome (Figs. 241, 244)

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Chapter 19

The Nervous System: Its Rôle in Surgical Practice

As the principal motivating and integrating force in the human organism, the nervous system assumes a position of truly first importance in surgical physiology. Only a few decades ago diseases were arbitrarily divided rather sharply into the "organic" and the "functional." This was gradually perceived to be at odds with the facts and there arose the discipline referred to as "psychosomatic medicine" which sought a common ground between diseases of the psyche and those of the soma. Now happily it is no longer necessary to consider the organic and the functional separately, for during the past few years it has been established once and for all that any given disease, "psychologic" or "organic," may affect the entire human organism. Disease of the psyche affects the soma and disease of the soma affects the psyche, the difference commonly being only one of degree. Derangement of motivation—of the emotions—results in diseases which frequently require surgical intervention; conversely patients with diseases of specific organs such as the liver, the adrenal or the colon frequently develop emotional problems which require psychiatric assistance. As another common example, excessive emotional stress of certain types can result in peptic ulcer for which surgery may be required; on the other hand, thyrotoxicosis, hyperinsulinism, Cushing's syndrome and Addison's disease are frequently associated with rather typical alterations of mood. The administration of adrenocortical steroids therapeutically may produce peptic ulceration or it may produce acute psychotic episodes (Fig. 246).

Above all, patients with diseases which must terminate fatally may develop marked psychiatric derangements, all due in one way or another to the disease. Among writers who have painted particularly vivid word pictures of such life circumstances are Shakespeare in numerous instances, Tolstoy in his *Death of Ivan Ilyitch*,[32] and Hemingway in his *Snows of Kilimanjaro*.[16] In brief, *the mind and the body are one*.

The nervous system will be considered under three headings: (1) Emotions and their visceral consequences: the autonomic nervous system. (2) Pain: pathways and management. (3) Increased intracranial pressure: pathophysiology and management.

Emotions and Their Visceral Consequences: The Autonomic Nervous System

The emotional composition of the human being is the final net result of an incredibly complex group of subtle and less subtle molding forces. Although man's immediate relationship to his actual physical and climatic environment has to do with his ultimate development, physical threats to his life and happiness are not so important to the present discussion as are the psychologic assaults, threats and frustrations which he encounters in his relationships with other human beings. One of the more penetrating studies regarding the problem of man's re-

action to his social and cultural environment was Wolff's *Stress and Disease* [37] He pointed out that man is particularly vulnerable because he is so constituted that he reacts not only to the actual existence of danger, *but to threats and symbols of danger experienced in his past that call forth reactions little different from those to the assault itself* Since his adaptive and protective capabilities are limited, a man's responses to many sorts of noxious agents and threats may be similar, the form of reaction to any one agent depending more on the individual's nature and past experience than upon the particular noxious agent evoking it Moreover, because of its magnitude and duration, the adaptive-protective reaction may be far more damaging to the individual than the effects of the noxious agent *per se* In this respect, the psychologic reaction to stress is not too different from the physiologic reaction to stress, which we have reviewed elsewhere That is, it was pointed out by Selye that the pituitary-adrenal system reacts to a wide variety of injuries by essentially the same endocrine response of the adrenal medulla, the pituitary, and the adrenal cortices though in varying degrees

A most important fact in any consideration of man's emotional problems is that "man is a tribal or group creature with a long period of development, dependent for his very existence on the aid, support, and encouragement of other men He lives his life so much in contact with men and in such concern about their expectations of him that perhaps the greatest threat of all is his doubt about his ability to live the life of a man He is threatened by those very forces in society upon which he is dependent for nourishment and life He must be a part of the tribe and yet he is driven to fulfill his own proclivities, because of his sensitive organization he is pulled two ways at the same time" [37]

Four generalizations were drawn by Wolff, on the basis of available data First, the "dangers" for man are in large part defined in the "mores," folklore and taboos of his specific culture Second, many of the "dangers" so defined are overstated or exaggerated so that the individual must deal with the anxiety imposed by his culture, plus the actual danger Third, along with such culturally engendered anxiety, methods for dealing with it are developed and prescribed by the culture These methods of resolution become formalized and are more or less effective in old and stable cultures Fourth, in changing or deteriorating cultures, the method of resolution of anxiety and tension ceases to be operative long before the tension-producing factors lose their potency In other words, when a culture either changes rapidly or deteriorates, the anxiety-resolving systems break down before the culturally engendered anxieties become attenuated To underscore this fact, it was noted that among the Hopi Indians, in recognition of the danger of snakes, it was decreed that one might not tread on the track of a snake If one did this, soreness of the ankles and legs would result In earlier days the accidental treading on a snake's track was promptly treated by the medicine man, who had a traditional procedure for neutralizing the untoward effects of the breach Among the younger Hopi, however, the taboo concerning the snake tracks persists, but their belief in the medicine man has been shaken by various influences of the present American civilization Thus, young Hopis who are unfortunate enough to step on a snake track often experience pain in the ankles, for which they now have at their command no satisfactory therapeutic procedure

Another example given concerned the rapid cultural changes now occurring in central India It has been reported that diarrhea, ulcerative colitis, neurocirculatory asthenia, and asthma are far more common among the relatively opulent, well nourished, hygienically oriented, educated, so-called Westernized Indians of the large communities than among the ignorant, unschooled, unhygienic, highly religious and often overworked, underfed, non-Western-

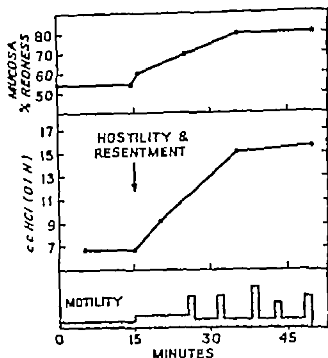


Fig 253 The stomach is traditionally influenced by emotions—"I have no stomach for that." Effects of emotion on gastric motility and blood supply of gastric mucosa are shown in the records of *observations on "Tom"* a patient with chronic gastric fistula *Upper record* Percentage redness of mucosa *Middle record* Gastric acidity in cubic centimeters of 0.1 N HCl per 100 cc of gastric juice. *Lower record* Motility of stomach In association with the feeling of hostility and resentment" there is an increase in gastric motility increase in volume of HCl secreted and increased vascularity of the gastric mucous membrane (From WOLF S., AND WOLFF H G Evidence on genesis of peptic ulcer in man J A. M A **120:** 670 1942 as modified by WRIGHT S *Applied Physiology* Ed. 9 London Oxford University Press, 1955)

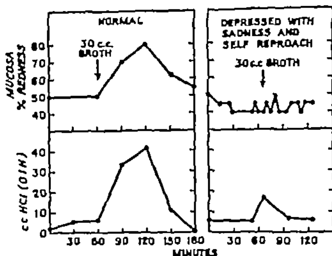


Fig 254 Peptic ulceration characteristically develops during periods of emotional stress. In these records of observations on "Tom" patient with chronic *gastric fistula are shown the effects of* emotion on gastric secretory response to food. *Records from above downwards* Percentage of redness of mucosa HCl secreted in cubic centimeters of 0.1 N HCl per 100 cc *Left figure* Changes in HCl secreted and vascularity of gastric mucosa (indicated as percentage redness) in response to ingestion of 30 cc of broth with the subject in a normal emotional state *Right figure* Reduced secretory and vascular response when the subject was "depressed with sadness and self-reproach" (From WOLF S AND WOLFF H. G Evidence on genesis of peptic ulcer in man. J A M A., **120:** 670 1942 as modified by WRIGHT S *Applied Physiology* Ed 9 London, Oxford University Press, 1955)

ized people of the small villages. The former are adjusting themselves to a new set of values and are caught between the two systems, finding little support in either Among these are the outwardly bland but inwardly striving dissatisfied, tense, anxious and hostile persons who exhibit offensive and defensive protective patterns.

When the individual feels insecure in his setting, there develop conflicts and feelings of frustration, anger, humiliation, and anxiety (Figs. 253 & 254) Once again "It is not the particular nature of the forces pressures and preferences that engender a threat for the individual in any particular society, but how they are perceived and the amount of conflict directly or indirectly engendered It is not the specific behavior towards parents, power possession, sexuality, the hours of work, or even the type of work or the amount of individual freedom of action, but it is the threat engendered by the culture which becomes pertinent to the development of stress with its ensuing protective reaction patterns and disease."[37]

Stress-Promoting Factors in the American Culture

Wolff reviewed the sociologic stress factors in the United States, and called attention to the fact that the conditions in the United States represent those of a country which has no long and subtle past upon which to base the methods of adaptation and resolution of conflicts. There is, as it were, a loss of the anchorage which was present in the countries from which our

forebears came, and yet the country is not old enough to have developed fixed cultural values and rigid strata of society Nevertheless, while it is frequently claimed that there are no social levels or "castes" in the United States, many sociologists have insisted that this is more of a misconception than a reality Actually, there are readily perceptible social strata in most communities, as was forcefully emphasized by J P Marquand in his novel *Point of No Return* [22]

Since an individual's reaction to his environment is frequently fixed very largely in early life, during his relationships within the home and with the parents, it is of interest to note that the frustrations and anxieties and conflicts engendered in the parents, by cultural pressures through which they have suffered frustration and rejection, are projected upon the children The parents' hostilities and their consequent limited capacity to give and accept love are features of their own insecurity and promptly reflect themselves in family relationships Children readily perceive when, for the parents, the "breath of life" is going out of a cultural institution concerning which the parents yet remain irresolute The phenomenon of children rejecting parents, and of parents rejecting the children and, frequently, each other, all threaten individual development, function, and happiness [37]

Examples of Subconscious Influences upon Measurable Bodily Functions

THE STOMACH AND DUODENUM Following the classic work of William Beaumont,[4] many studies have attested the fact that the gastric secretion and the appearance of the gastric mucosa can be made to vary in the individual For example, in one experimental subject with a gastric fistula through which the mucosa could be observed, it was found that sudden fear caused a decline in the secretion of hydrochloric acid and a marked blanching of the mucosa of the stomach In another situation, however, the same subject exhibited an increase in hydrochloric acid secretion in response to the evoking of feelings of hostility and resentment by offensive conversation [37]

Peptic ulceration has increased markedly among males since 1900 In studies involving patients outside the United States, Jennings[18] found that, between 1850 and 1900, of every 6 patients with peptic ulcers perforated into the peritoneal cavity, 4 were women and 2 were men Since 1920, of every 10 perforations, 1 has occurred in an elderly woman and 9 have occurred in men, mostly in the middle years or younger Similarly, a review[26] of the incidence of perforated ulcer at the New York Hospital from 1880 to 1900 revealed that women had perforated ulcer about as commonly as men, that is, 7 men to 6 women All perforations in these patients were visualized either at operation or at autopsy Beginning in the period from 1901 to 1906, however, the ratio of males to females was 10 males to 4 females, between 1932 and 1939 the ratio was 36 males to 3 females Therefore, it is apparent that perforated ulcers occurred frequently in young women during the middle of the nineteenth century and diminished markedly at the beginning of the twentieth century

The fact that the incidence has shifted from women to men during the last 50 years was examined from the point of view of the altered social requirements of the two sexes [18] It was suggested that the limited job opportunities open to women during the latter half of the nineteenth century, with heavy pressure to become married at an early age or to risk being an unwanted relative in another household, fostered much stress upon the female by strictly limiting her goals while denying her the release of overt expression of the competitive effort After marriage, also, the relationship between a man and a woman was well defined, with the man being unquestionably conceded the leading position in the household Nevertheless, he was permitted, within the security of the marriage, to lean heavily upon his wife emotionally

With the turn of the century, on the other

hand, women became much more able to seek employment outside the traditional teacher or similar positions, and their earning capacity increased so as to approach that of men. In present day marriages the woman often contributes to the financial structure of the family, and accordingly she assumes more liberty than was possible when she was not contributing to the family income. Moreover, she shares the prestige of earning for the family livelihood Yet, should she fail in her occupational venture, she is justified by society in retiring and of being provided for by her husband without occasioning comment. On the other hand, the man cannot retire, he must succeed, and if he fails to be "a good provider" he may be denied the feeling of security which his wife's emotional support could give him. Therefore, while society's requirements for the male are essentially as stringent as before, the emotional support accorded him in return has diminished. This is felt to be reflected in the overwhelming preponderance of peptic ulcer in males as compared with females.

THE COLON *Ulcerative colitis* Characteristically, the patient with ulcerative colitis is outwardly calm and superficially peaceful with more than the usual dependence upon some one person such as his mother or wife Nevertheless, it has been repeatedly found by psychiatric examination that this calm exterior is quite nonrepresentative of the intense feelings of hostility resentment and guilt going on in the subconscious mind or indeed, frequently in the conscious Furthermore it has been found quite often that the colon reacts to circumstances involving anxiety and other unpleasant emotions by excessive contraction mucosal engorgement, increased blood flow and an increased secretion of lysozyme

Functional megacolon It is well known that psychogenic constipation occurs in the adult, but it is not as generally appreciated that the megacolon seen in the child may be a psychologic reaction to his family or environmental circumstances rather than to the true absence of a normal complement of ganglia in the lower portion of the colon For this reason, it is important to question the parents carefully regarding the onset and development of the megacolon and constipation in the individual child

CARDIOVASCULAR SYSTEM. That circulatory symptoms may result from chronic anxiety and other psychic stress has been known for a great many years. The "soldier's heart," now usually known as "neurocirculatory asthenia" or "incoordination of the circulation," was described in the American Civil War by DaCosta.[6] Since that time, in all wars this syndrome has been prominent, consisting of sweating, faintness, easy fatigability, palpitation, extrasystoles and weakness, particularly under circumstances of prolonged danger Precordial pain is a prominent feature of this type of stress, and may be due to chronically increased tone of the pectoral and shoulder muscles and perhaps of the diaphragm Patients with cardiorespiratory symptoms often feel that it is impossible to take a deep breath

Of course, combat need not be the only cause of cardiopulmonary symptoms, since prolonged tension in the conduct of routine living may also result in these phenomena, as a result of anxiety, anger, guilt, rage, frustration and the like Patients who already have a diminished coronary circulation due to organic changes may develop outright angina at rest due to the effects of the tension state Changes in the efficiency of the renal circulation as a result of prolonged stress, may lead to arterial hypertension. Burdens imposed upon the heart by everyday physical exertions are often mild and usually brief in duration, and therefore are perhaps less costly to the individual than those associated with emotional disturbances which may be severe and prolonged over many months or even years Moreover, there is a tendency for patients with chronically increased cardiac work manifested by increased pulse rate and other circulatory phenomena eventually to develop organic heart disease, probably the

result of the long continued burden upon the heart It has been found that electrocardiograms made before and during an interview which involves topics of great personal significance may exhibit not only changes in rate and rhythm but alterations in the configuration of the action potential itself That is, in some patients the alterations in the electrocardiogram produced by psychic trauma and stress are similar, if not identical, to those produced by exercise

DIABETES MELLITUS When under emotional stress, patients with diabetes mellitus may escape from satisfactory control and develop acidosis unless more than the usual amount of insulin or dietary management is employed To be sure, under certain types of stress normal individuals exhibit glycosuria, probably because of an increased adrenocortical activity, with the usual diabetogenic tendency following such physiologic alterations

THYROID FUNCTION Following a severe emotional stress the basal metabolic rate may remain elevated for several days[24] Furthermore, the incidence of thyrotoxicosis has often been observed to rise in occupied countries, and many an instance of Graves' disease can be traced to a severe emotional shock such as loss of a close relative There is little doubt, in my mind, that psychic stress can have an effect upon thyroid function

ASTHMA Attacks of asthma may be provoked by emotional trauma Moreover, as noted above, respiratory symptoms commonly result from anxiety, hyperventilation being another example

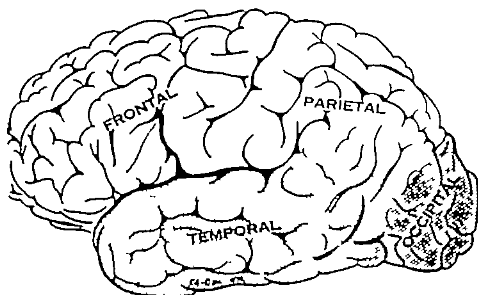
CONCLUSION Many additional examples of the influence of emotional insult upon bodily functions might be given, but the ones outlined serve to indicate the range and depth of these influences It may develop that, even in the same individual, one type of threatening situation may regularly cause extrasystoles, another type hypersecretion, and a third type diarrhea The brain is an incredibly subtle and complex receiving and transmitting instrument

The Autonomic Nervous System

The autonomic nervous system is a system of pathways from the cerebral cortex to the subcortical areas, to the hypothalamus, and thence to the viscera and the endocrine system—in broad outline

That a continuous neurohumoral pathway connects the cerebral cortex and the most remote viscera is no longer a matter of conjecture There has been increasing recognition of the existence of *widespread autonomic representation at the cortical level* in both man and animals, and certain data have been advanced to elucidate the functional interrelation between the two systems[20] The cerebral cortex (Fig 255) may be divided into two main regions first, the *neocortex*, comprising centers on the lateral surface and contiguous grey matter within its sulci, centers which function through projections to and from the lateral nuclei of the thalamus and also through connections with other parts of the cerebral hemispheres, and, second, the older *limbic system*, which is made up of a series of medial and orbital structures Thus, according to one classification, the elements included in the limbic system are (a) the pyriform area and cortex surrounding the olfactory striae, (b) the hippocampal gyrus, (c) the hippocampus, (d) the parasplenial gyrus, and (e) the subcallosal gyrus The subcortical nuclear structures known to be directly related to the limbic system include (a) the amygdala, (b) the anterior thalamic nuclei, (c) the hypothalamus, (d) the epithalamus, (e) parts of the basal ganglia, and (f) the pontine structures Various of these are shown in Figures 256 and 257

The limbic system—which serves as a conducting unit from the cerebral cortex to the hypothalamus and thence to the pituitary and to the autonomic nervous system—is thus made up of a group of functionally



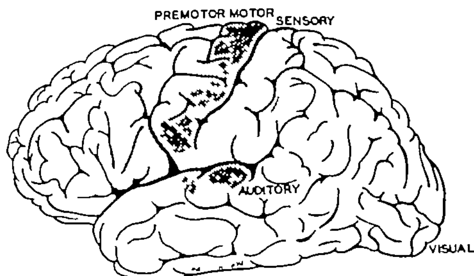


Fig 255 The lobes of the cerebral cortex (Modified from Klemme, R. M *Nursing Care of Neurosurgical Patients* Springfield, Ill., Charles C Thomas, 1940)

interrelated structures which send and receive projections to and from the medial nuclei of the thalamus and hypothalamus, a system which in early neural development is involved in affectively determined behavior[13] While no region of the cerebral cortex is exclusively concerned with any one function, and while the limbic system is predominantly autonomic in its affinities and the neocortex is predominantly somatic in each there is extensive overlapping, some autonomic responses are obtainable from the neocortex, and from the limbic system arise a limited number of reactions which affect somatic nervous elements.

In brief, the limbic system is primarily concerned with the visceral nervous functions and the neocortex with somatic nervous functions

HYPOTHALAMUS INTEGRATIVE CENTER OF THE AUTONOMIC NERVOUS SYSTEM. It would be difficult to overestimate the importance of the hypothalamus to the physiologic mechanisms considered in this volume The hypothalamus was called by Sherrington[29] the head ganglion' of the body Its anatomic

connections with the cerebral cortex (neocortex as well as the limbic system) are extensive, and it is a region of the forebrain in which autonomic and somatic function

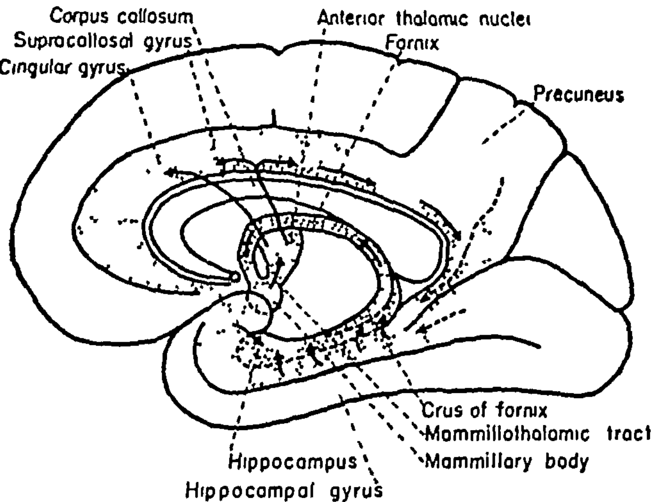


Fig 256 Some elements of the limbic system The subcortical areas *adjoining the cingulate* gyrus have rich connections which mediate emotional and hence visceral responses (From Kuntz, A *Visceral Innervation and Its Relation to Personality* Springfield, Ill, Charles C Thomas, 1951)

overlap *The hypothalamus functions in relation to the limbic system in much the same way that the thalamus itself does to the neocortex,* for the hypothalamus has its own afferent system ascending from the spinal and the medullary levels, and in turn it projects to the cortex [20]

In Figure 257 are shown certain of the more important connecting pathways of the hypothalamus, which is in the neighborhood of the mammillary body in this diagram It is to be noted that the hypothalamus is joined through other thalamic nuclei with the cerebral cortex and, in particular, with the structures of the limbic system (cingulate gyrus) Furthermore, the hypothalamus is associated with ascending and descending tracts that pass through the medulla oblongata These pathways continue down the spinal cord and give rise to the preganglionic and postganglionic fibers which innervate the viscera and blood vessels (Fig 258)

Fig 257 Through the hypothalamic pathways the higher centers of the cerebral cortex influence the function of thoracic and abdominal viscera (From Kuntz, A *Visceral Innervation and Its Relation to Personality* Springfield, Ill, Charles C Thomas, 1951)

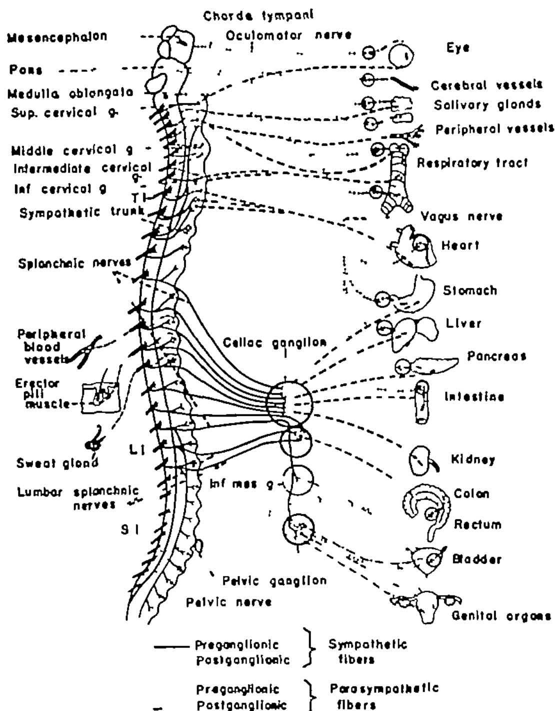


Fig 258 Emotional responses are mediated largely through the autonomic nervous system (From KUNTZ, A *Visceral Innervation and Its Relation to Personality* Springfield Ill Charles C Thomas, 1951)

Rôle of hypothalamus and surrounding areas in metabolism The hypothalamus and bordering nervous structures comprise one of the most fascinating regions of the entire body Let us refer again to Figures 20, 256 and 257 for orientation. The hypothalamus is at the level of the diencephalon. In the medulla oblongata and the pons are found centers which have to do with the regulation of vasomotor activity and respiration, and there appears to exist a center in the medulla oblongata which exerts an influence on carbohydrate metabolism.[20] Nevertheless the center in the medulla that has to do with carbohydrate metabolism is less important than the neural mechanisms for the control of carbohydrate metabolism which are located in the hypothalamus (but which connect with the center in the medulla)

The functions of the hypothalamus Integration and emotional response —Much

of the foregoing discussion has had to do with the rôle of the hypothalamus as a "switchboard" or "clearing center" for impulses having to do with the expression of emotion and personality Let us now consider its function in metabolism

Regulation of pituitary secretions —In Figure 20 are shown the neural connections which exist between the hypothalamus and the hypophysis In addition, it is considered probable that humoral influences also act directly upon the hypophysis [17] The rate of release of ACTH, the posterior pituitary antidiuretic hormone, and certain other hormones of the anterior lobe of the pituitary appear to be regulated by impulses descending to this gland from the hypothalamus

Homeostasis —The maintenance of the "steady state," so necessary for normal function of the organs of man and other warm-blooded animals, is achieved in considerable measure through the integrative functions of the hypothalamus Lesions of this organ result in marked deviations from normal physiologic function in a variety of ways The hypothalamus has to do with the regulation of *body temperature,* and specific lesions produced in this area may result in marked hyperthermia or, under other circumstances, in hypothermia The prominent rôle of the hypothalamus in *water and salt metabolism* has been recognized for many years, and the most marked aberration in this connection is the diabetes insipidus produced by some lesions in this region The classic work of Verney[33] did much toward defining the relationships which exist between the hypothalamus, by way of the hypothalamico-hypophyseal tract, and secretion by the posterior pituitary of the antidiuretic hormone In addition, as noted, impulses from the hypothalamus aid in regulating the secretion of ACTH, which in turn regulates secretion of adrenocortical hormones with their far-reaching effects on body fluid metabolism

Carbohydrate, protein, and fat metabolism —It is not necessary to describe in detail specific hypothalamic effects on the metabolism of these foodstuffs Merely through its effect on the secretion of ACTH, this integrative center exerts an effect on all However, it is of interest here to note the relation of hypothalamic lesions to obesity Anand and Brobeck[1] confirmed that in rats and cats an increased food intake and obesity resulted from chronic bilateral destruction in the vicinity of the ventromedial nuclei of the hypothalamus, they also found that the production of bilateral lesions in the lateral hypothalamic area caused the animals to refuse to eat Even in animals previously made hyperphagic by medial lesions, eating ceased when the lateral areas were destroyed bilaterally It was therefore assumed that the lateral areas contain a "feeding center" responsible for the central hunger reaction or the urge to eat, while the more medial regions may be capable of exerting normally an inhibitory control over the feeding desire

Andersson and McCann[3] stimulated the hypothalamus of the goat and recorded with convincing movies the effectiveness of either an electrical current or the injection of a small amount of hypertonic solution in increasing the water intake of the animal Andersson[2] showed that the stimulation of the anterior hypothalamus in the vicinity of the supraoptic nucleus would induce milk ejection in lactating sheep and goats and, further, that the mechanism was mediated by the neurohypophysis Moreover, it was pointed out that procedures known to release the posterior lobe hormone, such as intracarotid injections of hypertonic saline solution or stimulation of the central vagus, also induce milk flow This is of course of interest in psychic and other problems attendant upon human lactation De Groot and Harris[11] showed that electrical stimulation in the region of the tuber cinereum or the mammillary bodies in unanesthetized, unrestrained rabbits resulted in lymphopenia comparable in magnitude to that caused by emotional stress The lymphopenic response is regarded as one of the

ckest known indicators of pituitary ac
ity

There is evidence that the hypothalamus o influences not only the gastric, but pancreatic and biliary functions as well

The waking state and sleep —It has been own for many years that the neural chanisms in the region of the hypothala s have a rôle in the maintenance of the king state Either somnolence or exces- e activation and excitation can be pro- ced by appropriate lesions in animals and tain clinical hypothalamic syndromes are ociated with excessive sleeping

The hypothalamus and pulmonary ema —Gamble and Patton[14] reviewed the dence that neural mechanisms are in lved in the genesis of pulmonary edema ey noted that there is a high incidence lung edema in head injury cases and that ntral nervous system depressants auto- mic blocking agents, or denervation pro- dures protect against some of the edema nic procedures The experimental pro ction of pulmonary edema by contusion d increased intracranial pressure was con lered further presumptive evidence of a ural pathogenesis for some instances of lmonary edema Furthermore they them ves were able to produce fatal hemor- agic edema of the lungs in rats by discrete ectrolytic lesions of the rostral hypothala us The edema was confirmed by gravi etric procedures and by both gross and stologic study of the lungs

Clinical hypothalamic syndromes Since ost of the evidence which has been given ove was derived from experiments on imals, *it is of confirmatory interest to* ote that such clinical circumstances also cur in human beings Wechsler[34] reviewed rtain of the groups of findings which he ad observed clinically and which he con dered to be due to lesions of the hypo- alamus and surrounding parts of the ain Among these manifestations were mptoms reflecting interference with tem erature regulation variations in blood essure in pulse and respiratory rates, dis- turbances in water and sugar metabolism, and peculiar states of consciousness Not all patients presented all these findings, but most had deviations in one or the other of the following sleep, emotional expression, and other states of consciousness, water, fat, and sugar metabolism, vasomotor ac tivities such as blood pressure and pulse rate, *body temperature, and gastrointesti* nal activity

There is clinical evidence that destructive lesions at brain levels above that of the hypothalamus may produce metabolic changes

CLINICAL CLASSIFICATION OF AUTONOMIC DYSFUNCTION Before proceeding to con- sideration of the specific innervation of various of the viscera *via* the sympathetic and parasympathetic nerves it is useful to consider at this point some of the conditions which have been considered to be caused by autonomic dysfunction A classification is given in Table 22 While the autonomic nervous system may not be responsible for the development of all these conditions in all patients there can be little question but that dysfunction of the autonomic nervous system central or peripheral can result in most of them *If nothing else*, the classifica tion serves to indicate the tremendous range of bodily functions which are influenced, if indeed not regulated, by the autonomic nervous system

PERIPHERAL DISTRIBUTION OF SYMPATHETIC AND PARASYMPATHETIC NERVES In Figure 258 is shown the innervation of various of the body organs by the sympathetic and para- sympathetic nerves The number of auto- *nomic nerve fibers that* enter most of the visceral organs leaves little doubt that the autonomic nervous system influences their function In addition humoral factors and an intrinsic nerve supply are also operative in some organs

Familial autonomic dysfunction Riley[28] reviewed 33 cases of what he termed fa milial autonomic dysfunction The most striking features in these children were de- fective lacrimation in *that they failed to*

TABLE 22 A CLINICAL CLASSIFICATION OF DYSFUNCTIONS OF THE AUTONOMIC NERVOUS SYSTEM*

Central dysfunctions
- I Organic
  - A Hypothalamic
    - 1 Disturbed temperature regulation
    - 2 Autonomic epilepsy (Penfield)
- II Emotional
  - A Cardiovascular
    - 1 Neurocirculatory asthenia
    - 2 Arrhythmias
    - 3 Tachycardia
    - 4 Bradycardia
    - 5 Syncope
    - 6 Blush
    - 7 Hypertension
    - 8 Emotional vasoconstriction
  - B Genitourinary
    - 1 Polyuria
    - 2 Emotional albuminuria
    - 3 Amenorrhea
  - C Gastrointestinal
    - 1 Pylorospasm
    - 2 Peptic ulcer
    - 3 Ulcerative colitis
    - 4 Nausea, vomiting, diarrhea
  - D Metabolic
    - 1 Emotional hyperglycemia
    - 2 Hyperventilation syndrome
    - 3 Diabetic acidosis

Peripheral efferent dysfunctions (possible)
- I Sympathetic hypertonia
  - A Skin—hyperhidrosis
  - B Eye and ear
  - C Gastrointestinal
    - 1 Ileus
    - 2 Megacolon
    - 3 Postvagotomy atony
  - D Cardiovascular
    - 1 Sinus tachycardia
    - 2 Raynaud's disease
    - 3 Raynaud's phenomenon
    - 4 Scleroderma sclerodactyly
    - 5 Livedo reticularis
    - 6 "Reflex" peripheral vasoconstriction
      - (a) Thrombophlebitis
      - (b) Peripheral emboli and thrombosis
      - (c) Cervical rib, scalenus anticus syndrome
      - (d) Shoulder-hand syndrome (myocardial infarction)
- II Sympathetic hypotonia
  - A Eye—Horner's syndrome
  - B Cardiovascular
    - 1 Postural hypotension
  - C Genitourinary—impotency (male)

TABLE 22—*Cont'd*

- III Parasympathetic hypertonia
  - A Respiratory—bronchoconstriction
  - B Gastrointestinal
    - 1 Postsympathectomy ulcers
    - 2 Pylorospasm
    - 3 Spastic constipation
    - 4 Peptic ulcer
- IV Autonomic dystonia
  - A Skin
    - 1 Erythromelalgia
    - 2 Acrocyanosis
  - B Gastrointestinal—cardiospasm (absence of intrinsic ganglia)
  - C Genitourinary—neurogenic bladder

Peripheral afferent dysfunctions
- I Syndromes characterized by pain
  - A Causalgia and Sudeck's atrophy
  - B Angina pectoris
  - C Herpes zoster
  - D Shoulder-hand syndrome
  - E Dysmenorrhea (?)
- II Reflex dysfunctions
  - A Carotid sinus syndrome
  - B Vagovagal syndromes
  - C Pulmonary edema

* Collected from the literature

produce tears in normal fashion when crying This was usually absolute, but in several cases an occasional tear was visible Nevertheless, the eyes were not dry and tear production was adequate to maintain corneal health in most instances Another prominent feature was skin blotching, and in all but 1 of the group erythematous, sharply defined blotches appeared on the face, shoulders, and upper part of the thorax when the patient was excited or was eating They were usually symmetrical and tended to recur in the same areas One patient showed only mottling of the extremities when excited Excessive perspiration was another prominent feature in that all patients perspired excessively, especially under conditions of excitement Another patient exhibited a symmetrical skin blotching but also a symmetrical perspiration Other findings consisted of (1) drooling which persisted long past infancy, (2) emotional instability in that they responded to minor emotional stimuli in an "all or none"

fashion, (3) motor incoordination with hyporeflexia, and (4) relative indifference to pain The familial incidence was considered to suggest a genetic origin of this syndrome

FUNCTIONAL COMPONENTS OF AUTONOMIC NERVES The sympathetic and the parasympathetic system each contain both afferent and efferent fibers, and these fibers of course supply the motor and sensory components of visceral innervation Moreover both systems have preganglionic and postganglionic fibers (Fig 259) Unlike the peripheral somatic efferent conduction pathways the peripheral visceral efferent pathways involve synaptic relays in autonomic ganglia. The conduction of impulses through the preganglionic fibers results in the liberation of an humoral substance at the synaptic junctions in the ganglia. The conduction of impulses through the postganglionic fibers likewise results in the liberation of an humoral substance at the neuro effector junctions. It is considered that these humoral substances play a part in synaptic transmission and also in transmission at the neuro effector junctions. *The humoral substance liberated by stimulation of postganglionic sympathetic fibers re*

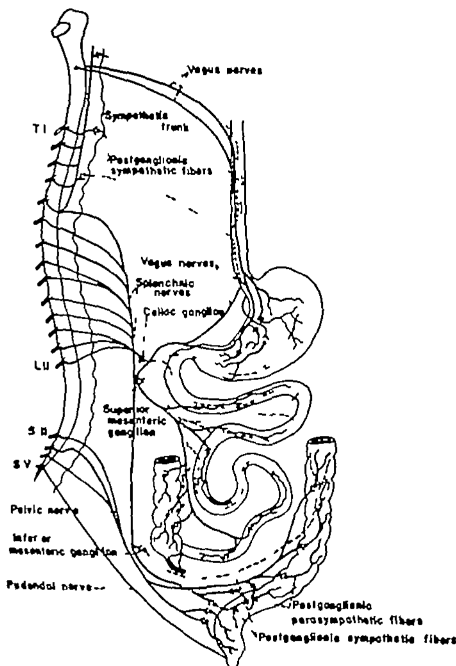
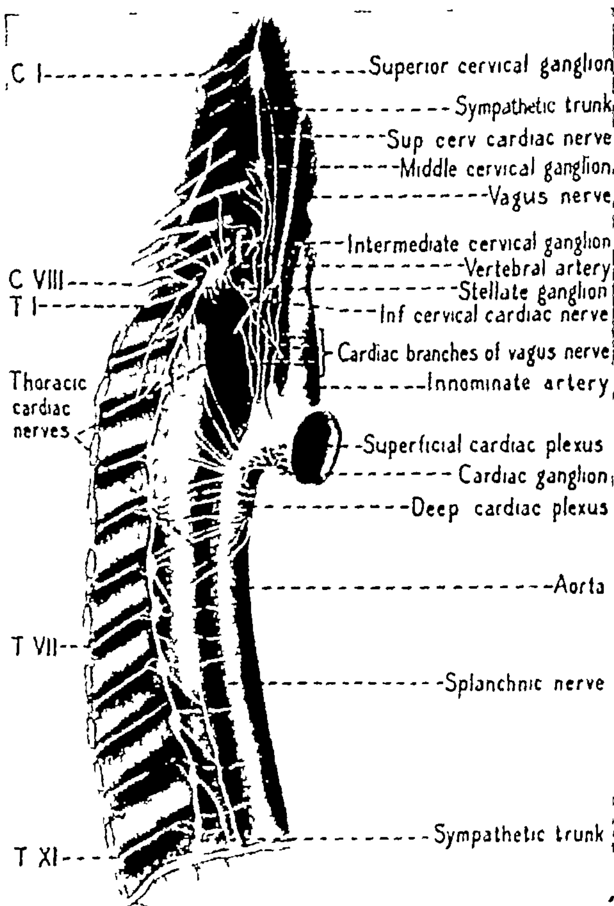


Fig 259 Innervation of the alimentary tract. (From KUNTZ, A. *Visceral Innervation and Its Relation to Personality* Springfield, Ill Charles C Thomas 1951)

sembles adrenin, if it is not identical with this substance Since it is intimately associated with sympathetic nerve stimulation and function, it has been termed *sympathin* Kuntz[20] emphasized that the entrance of this material into the circulating blood with its epinephrine-like effects may be responsible for the generalized response observed in sympathetic stimulation In contrast, *the humoral substance that is liberated by stimulation of postganglionic parasympathetic fibers possesses properties in common with acetylcholine* but probably is not identical with that substance Since this substance, like acetylcholine, is highly unstable, it exerts only a local influence Finally, the humoral substance liberated at synaptic junctions due to the stimulation of either sympathetic or parasympathetic preganglionic fibers appears to be identical with parasympathin, the acetylcholine-like substance

SURGERY OF THE AUTONOMIC NERVOUS SYSTEM *The vascular system* Raynaud's syndrome —The use of sympathectomy in the management of Raynaud's disease or other conditions manifesting Raynaud's phenomenon was described previously (p 421) In Figure 260 are shown the relationships of the upper sympathetic ganglia to the spinal nerves in the upper extremity It is our personal feeling that the results achieved by sympathectomy in Raynaud's-like conditions are best produced by a liberal resection of the stellate ganglion and a portion of the chain above and below it This of course removes both preganglionic and postganglionic sympathetic fibers, with the possible appearance of the so-called "sensitivity phenomenon" due to an increased susceptibility of the end organs to circulating epinephrine However, this has always been, to us, a difficult matter to prove clinically, and we no longer attempt to spare the postganglionic components Hor-



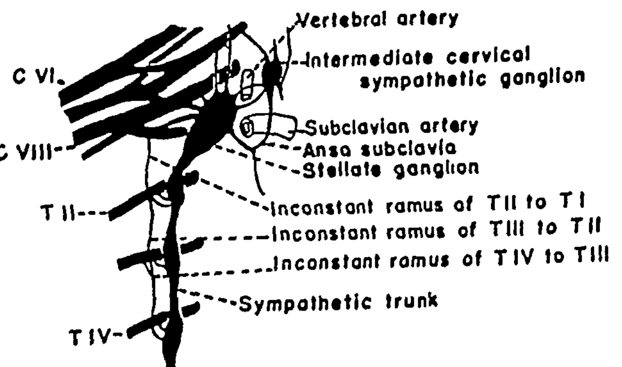


Fig 260 Sympathetic innervation of the upper extremity (From KUNTZ, A *Visceral Innervation and Its Relation to Personality* Springfield, Ill, Charles C Thomas, 1951)

ner's syndrome is usually produced by this type of operation.

Shoulder hand syndrome.—It is not always appreciated that shoulder injuries, as well as the sequelae of myocardial infarction, may result in peculiar alterations in the upper extremity, affecting in particular the hand. There may be burning pain in the part associated with swelling and occasionally, some atrophy of the intrinsic musculature of the extremity. Bone changes have also been described. We have cited (p. 451) the case of an enlisted man who fell while carrying a case of beer to the officers' club, injuring his right shoulder. Following a rather painful recovery he exercised by suspending his weight by the involved hand and arm. The shoulder was again injured. Again it improved gradually, but there developed a burning type of pain in the forearm and hand of that extremity associated with swelling of the hand and wrist. There was no alteration in the sensation to touch and pin prick and there was no loss of muscular power except that due to the pain induced by muscular contractions. Roentgen examination revealed no demonstrable abnormality. It was considered probable that he had somehow injured the sympathetic outflow into the right arm.

The heart.—The innervation of the heart is shown in Figure 132. Both the parasympathetic vagus nerves and the sympathetic nerves play an important rôle in the rate and character of cardiac contraction. Cardiac acceleration is mediated through the sympathetic nerves and cardiac inhibition through the vagus nerves. Fainting (syncope) may be associated with a marked increase in vagal tone and a markedly slowed heart rate in the neighborhood of from 40 to 50 beats per minute. Apprehension causes sympathetic release and rapid heart action. Sympathetic denervation as treatment for angina pectoris has largely been abandoned.

Carotid sinus syndrome.—The carotid sinus and the area of the aortic arch have much to do with the reflex control of blood pressure (p. 355) which is mediated through the autonomic nervous system; there is an increase in heart rate and peripheral vasoconstriction. The opposite effects occur in acute distention of the carotid sinus.

Clinically, *carotid sinus syncope* is due to the sensitivity of the carotid sinus to pressure, perhaps from a stiff collar when the person turns his head in one direction or the other. As a result of the pressure stimulation of the carotid sinus, there may be a sudden slowing of the heart mediated through stimulation of the vagus nerve and perhaps suppression of the sympathetic system with the consequence that the individual faints. The treatment for this condition is to strip the adventitia of the carotid bifurcation on the involved side, which is determined preoperatively by clinical studies involving carotid sinus pressure and reproduction of the syndrome of syncope. All adventitia, with nerves, is stripped for from 2 cm. below the bifurcation to approximately 2 cm. above, on both the internal and the external carotid arteries. It is well to infiltrate the carotid sinus area with 2 per cent procaine before beginning dissection. In case of doubt as to which side is at fault, both sinuses should be denervated.

Vessels of the lower extremities.—Lumbar sympathectomy has had an extensive trial for a wide variety of peripheral vascular conditions (see Chapter 15). The best results have been realized in Buerger's disease and in causalgia following traumatic arterial injury. In fact, almost by definition the pain ascribed to 'causalgia' must be relieved by sympathetic block or division else the diagnosis of causalgia becomes suspect. Sympathectomy in other vascular conditions has also been discussed elsewhere.

Sympathectomy for arterial hypertension.—This particular mode of treatment has now had a wide clinical application. The consensus is that while a few patients are considerably benefited and others somewhat improved symptomatically if not af-

forded increased longevity, the unpredictability of the response of the individual patient and the questionable effect in extending longevity have resulted in the virtual abandonment of this treatment.

The same hypotensive effects can be achieved by conservative therapy in employing autonomic blocking agents such as hexamethonium and other antihypertensive agents. If sympathectomy is to be used at all, it should probably be reserved for the very occasional patient whose hypertension does not respond to medical measures and whose condition is rapidly deteriorating.

The respiratory tract. The respiratory tract—and in particular the lungs—receives a rich supply of both sympathetic and parasympathetic fibers. In general the parasympathetic nerves exert a tonic or constrictor influence on the smooth muscle of the bronchioles, whereas the sympathetic nerves are mainly inhibitory. The respiratory function is closely coordinated with changes in the circulation; this is achieved through the carotid sinus reflexes and similar pressor reflexes in the aortic arch.

The autonomic nerves have been assigned a rôle in the physiologic mechanisms acting in bronchial asthma, in pulmonary emphysema where bronchial spasm and stenosis exist, and in the mechanism of death in pulmonary embolism. Yet, despite considerable clinical application of pulmonary neurectomy, there is still, in our opinion, inadequate evidence that sufficient beneficial effects are achieved by nerve division in these conditions to warrant routine surgery.

The gastrointestinal tract. The esophagus.—The esophagus is supplied by both vagal and sympathetic fibers. The act of swallowing, once it has been initiated, is reflex and apparently depends, in part, upon a deglutition center in the medulla oblongata. That the number of ganglion cells may be diminished in the presence of megaesophagus has been reported from time to time, and the possibility that achalasia (cardiospasm) is the result of autonomic dysfunction has been suggested by many. However, this concept of the etiology of achalasia or dysfunction of the cardioesophageal sphincter has never been sufficiently well documented to achieve general acceptance, and at the present time autonomic surgery has no prominent place in the management of esophageal disease.

The stomach.—The stomach receives both sympathetic and parasympathetic nerve fibers. By and large, the stimulation of the vagus nerves results in increased gastric motility and secretion. Gastric motility tends to be inhibited by stimulation of the splanchnic sympathetic nerves. Even so, the response to the stimulation of either group of nerves may be conditioned by the previous state of activity of the gastric musculature.

The important surgical aspects of the vagal supply of the stomach were discussed in connection with the use of vagotomy in the treatment of peptic ulcer (p. 314).

The small intestine.—As a rule, stimulation of the parasympathetic nerves to the small intestine results in augmentation of muscular tone and motility, whereas stimulation of the sympathetics tends to have an inhibitory effect. It was seen earlier that anger, guilt, hostility, and resentment may be accompanied by an increased motility of the large intestine and by an increased secretion of mucus. Conversely, intense fear or fright frequently is accompanied by relaxation of the large bowel and ischemia of the mucous membrane. It was reported by Lillehei[21] that extirpation of the celiac and the superior and inferior mesenteric ganglia in dogs regularly resulted in fulminating diarrhea associated with bloody stools containing increased amounts of mucus; frequently peptic ulceration in the stomach and the duodenum also occurred. However, when vagotomy was carried out simultaneously with the extirpation of these ganglia, peptic ulceration and gastroenteritis failed to develop. For this and similar reasons, Dennis and his associates[12] used vagotomy as a treatment for ulcerative colitis, the rationale being that the intestinal hypermotility



Fig 261 Autonomic ganglia in intestine (*A*) Sympathetic trunk ganglion of a child 8 years of age (*B*) celiac ganglion of an adult. (From KUNTZ A *Visceral Innervation and Its Relation to Personality* Springfield, Ill., Charles C Thomas, 1951)

Lower left Hirschsprung's disease This condition is due to inadequate numbers of autonomic ganglia in the distal constricted segment

and diarrhea would be diminished by abolishing the vagal nerve supply Unfortunately, this did not prove particularly helpful in the management of ulcerative colitis

The colon —True congenital megacolon has been mentioned elsewhere but certain facts bear repeating here The marked proximal dilatation with the normal sized distal lower segment and rectum, has excited much interest in the extrinsic and intrinsic nerve supply to this organ. Through the work of Swenson and his associates [31] it was pointed out that the normal sized segment was usually deficient in ganglion cells (Fig. 261) Since the distended portion of the bowel was found frequently to have a normal number of ganglion cells it was assumed that the diseased portion of the bowel was actually the distal and normal sized portion, which merely failed to propel the fecal stream from the distended portion of the colon to the anus. One of the first forms of surgical treatment was resection of the distended portion of the colon which at that time appeared to be the segment at fault however, few were improved Next there was a period during which sympathectomy was performed with the thought that the inhibitory influence of the sympathetic nerves to the colon would be abolished and that the parasympathetic (pelvic) nerves would thus be unopposed However, it was not until Swenson's demonstration that the site of pathologic function was in the distal segment that the operation of excising the distal segment and anastomosing the normally innervated colon to the distal rectum was devised this represented a major advance in the management of congenital megacolon. At the time of operation it is important to monitor the extent of colon resection by means of frozen section demonstration of ganglia in the bowel wall at the level of proximal transection Of course rarely there may be a relative paucity of ganglia throughout the entire gastrointestinal tract.

It might be mentioned here that megacolon may be associated with megaureter, probably through the same general deficiency of intrinsic innervation

Pain

Nature and Types of Pain

The sensation of pain is often not only the symptom which signals to the patient that he should consult a physician but it is also a manifestation of the disease that may greatly facilitate diagnosis For pain to occur, however, the proper stimulus must be present To give an example, pain arises from the bowel not when it is cut but when it is stretched, in contrast, stretching of the skin does not usually cause pain but cutting does

Pain is an unpleasant sensation that may be derived from actual physical injury or from a state of mind. In this connection, it at times becomes almost impossible to determine whether or not the pain which the person complains of is due to a disorder of the mind or to a disorder of a visceral or somatic portion of the body By the technic of counterirritation, pain from a part can be successfully diminished if not abolished, at least in the mind of the patient The procedure known as "cupping" was formerly employed fairly extensively as a counterirritant, as have been hot water bottles, mustard plasters, and other means of causing strong stimulation of the skin sensory receptors to distract the patient from the perception of deeper "pain" The importance of the state of consciousness and frame of mind upon the perception of pain and its intensity, as reported by the patient, may be still further emphasized by the fact that reassurance often results in the relief of the pain in a particular situation Similarly, pain is notoriously worse at night, though often no specific reason can be determined "In the light of day" many of the fears, apprehensions, and unpleasant memories experienced during the night—and which may have summated to increase the patient's "pain"—are dissipated by the realization that painful past experiences are, in fact, past in time if not in memory

Though pain may have a strong psychic or emotional component, this does not by any means negate the fact that it is a definite entity and that all the discomfort is quite real to the patient

How is pain mediated? It is generally accepted that basic pain perception is mediated through specific pain receptors which consist of naked nerve endings in the skin or elsewhere Thus, pain may be perceived independent of other sensations such as touch or heat Nevertheless, if the nerve fibers which conduct these other sensations, such as heat or touch, are sufficiently strongly stimulated, the resulting sensation may be an unpleasant one and may be considered pain Therefore, pain may be mediated through both myelinated and unmyelinated fibers The impulses enter the spinal cord and travel over the spinothalamic tracts to the brain stem, and thence to the posterolateral and posteromedial nuclei of the thalamus Awareness of pain seems to take place at the thalamic level, but the cerebral cortex appears to be required for localization and recognition of the quality and degree of the offending stimulus

It has been pointed out that somatic pain from the body surfaces provokes a so-called defense reaction consisting of an increase in the output of epinephrine with consequent cardiac acceleration, an increase in blood pressure, and vasoconstriction Visceral pain, in contrast, may lead to almost opposite effects, in that there is a decrease in blood pressure and a decrease in heart rate, and nausea and vomiting may occur Certain types of pain may be considered defense mechanisms, such as the warning pain of angina and intermittent claudication, signaling that ischemia of the part requires reduced muscular activity On the other hand, Corbin[6] has emphasized that causalgic pain and neuralgic pain are difficult to explain on a teleologic basis, since the persistence of such pain over a long period of time may result in serious deterioration of the individual's emotional stability—as physicians well appreciate

SUPERFICIAL PAIN Superficial pain is the pain that is elicited by noxious stimuli at

the skin surface. It is clearly localized and it is sharp or burning When greater than the usual stimulus is required to elicit pain, *hypesthesia* is said to exist, if the part is unduly sensitive, then *hyperesthesia* (or hyperalgesia) is the term used to describe this state. Spontaneous sensations which are unpleasant may occur in the skin, such as itching, *formication, or tickling*

The increased sensitivity or hyperalgesia of the skin deserves further comment. It frequently accompanies febrile illnesses, but it may be caused by diseases of the nerves themselves, as in neuritis whether due to trauma or other cause It often is noted on either side of a surgical wound particularly following a subcostal incision for cholecystectomy, as the intercostal nerves begin to regenerate the edges of the wound are at first relatively insensitive to stimuli but presently the skin may become acutely sensitive, gradually resuming the normal state with the passage of time

DEEP PAIN An example of deep pain is that pain which is felt in bones. It is a dull, aching, diffuse and often purely localized sensation Periostitis, ischemia, or distention of the marrow cavity may cause deep pain In the days when intramarrow infusions were relatively popular, the injection of blood or other fluid into the marrow space of the tibia at too rapid a rate resulted in distention of the marrow cavity and outcries of pain.

A second type of deep pain is visceral pain, *which is usually dull and is poorly* localized This type of pain may be produced by various stimuli such as inflammation within the abdomen, distention of hollow viscera, or traction on the mesentery of the bowel.

REFERRED PAIN This is the familiar phenomenon observed when irritation of the diaphragm by a subdiaphragmatic collection results in pain over the trapezius or the deltoid region. The reason for this is, of course, that the sensory area of the shoulder "referred to" is supplied by the same cervical

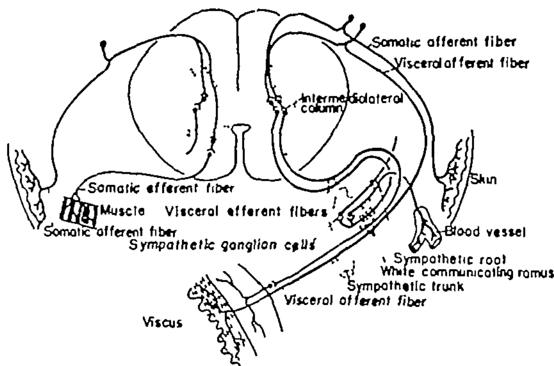


Fig 262 Mechanism of referred pain from abdominal viscera. (From KUNTZ, A *Visceral Innervation and Its Relation to Personality* Springfield Ill Charles C Thomas, 1951)

nerve roots which supply the phrenic nerve to the diaphragm Similarly, pain in the hip joint, as in early tuberculosis, may be referred to the knee Or, pain due to coronary occlusion may be referred, by way of sympathetic connections, down the inner surface of the left arm The reflex arc, by means of which intraperitoneal visceral pain is referred to the skin of the abdominal wall, is shown in Figure 262

CENTRAL PAIN Corbin[6] calls attention also to central pain, which is that perceived in the mind when there is no peripheral cause, at least at the moment One of the most classic examples of this type of phenomenon is the so-called phantom limb pain which was described by S Weir Mitchell and his associates[25] a great many years ago For months following amputation the patient may "experience" pain in the amputated foot—even though he sees that the foot is gone

TABLE 23 APPROXIMATE PAIN REFERENCE OF VARIOUS ORGANS IN MOST INSTANCES

1	Esophagus—to anterior or posterior thorax at about the level of the lesion, in many patients
2	Heart—to precordium, neck (and, rarely, teeth), left arm, shoulder blades, or epigastrium
3	Diaphragm—to deltoid region on involved side
4	Stomach—epigastrium, characteristically, pain of ruptured ulcer tends to spread downward
5	Pancreas—belt-like area, front and back (Fig 86, p 252), pain of hemorrhagic pancreatitis tends to spread downward
6	Gallbladder—to right subcostal region anteriorly and to shoulder blades posteriorly, may cause precordial pain simulating angina pectoris
7	Kidney and ureter—to back or flank, or into genitalia on the involved side
8	Bladder—suprapubic pain or into genitalia
9	Ovary, tube or uterus—to anterior abdomen, often suprapubic, or into groin
10	Appendiceal—often begins adjacent to umbilicus but usually localizes in right lower quadrant
11	Bowel—depends on the level, cramping pain should always suggest mechanical obstruction, diverticulitis may simulate left sided appendicitis
12	Pancreatic, gallbladder, or gastroenterostomy dysfunction (stomal ulcer)—may be the cause of pain referred to the back in patients with these possibilities

ABDOMINAL PAIN The accurate interpretation of the origin and character of abdominal pain represents a major requirement in the successful conduct of abdominal surgery The type of pain which arises from disease of various organs has been mentioned under appropriate sections throughout this volume, but certain important relationships are shown in Figure 262 and Table 23

Surgical Procedures for Relief of Pain

In Figure 263 are shown the levels at which various surgical procedures may be performed for the relief of pain These include operations upon the cerebrum, chordotomy in both the cervical and the thoracic regions, myelotomy of the lower cord, and sympathectomy However, extensive thoracolumbar sympathectomy carries with it the hazard that subsequent serious disease, such as a ruptured peptic ulcer or gallbladder, may cause no symptoms

The Use of Opiates for Pain Relief

Patients vary widely in the degree to which they experience or manifest pain following operation Actually, the wound is usually not especially painful unless motion is involved, as with thoracic incisions Therefore, heavy doses of opiates, which depress respiration, are best avoided unless obviously required

Increased Intracranial Pressure: Pathophysiology and Management

The Third Circulation: Origin, Course, and Absorption of the Cerebrospinal Fluid

In delivering his Cameron Prize Lectures at the University of Edinburgh, October 19–22, 1925, Harvey Cushing dedicated the first to Francois Magendie and entitled this lecture "The Third Circulation and Its

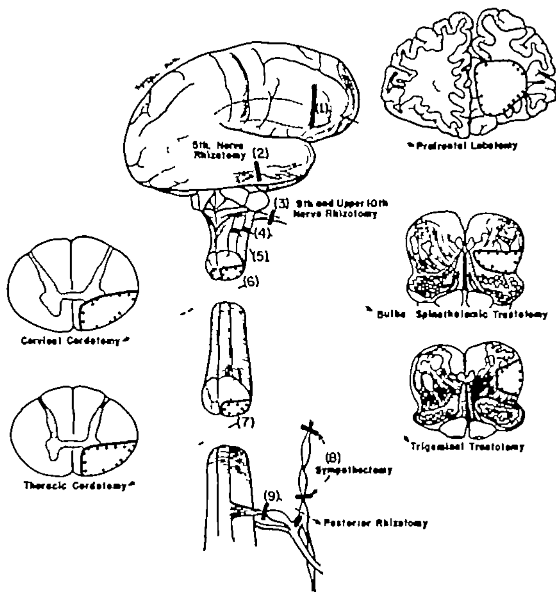


Fig 263 Surgery of pain relief Sites of standard neurosurgical procedures for relief of pain The IXth Xth and XIth nerves leave the brain stem along a line dorsal to which lies the descending trigeminal tract (incision 5) and ventral to which lies the crossed pain pathway from the limbs and the torso (incision 4) (From SWEET W H In *Surgery—Principles and Practice* edited by J G Allen H N Harkins, C A Moyer and J E. Rhoads Philadelphia J B Lippincott Company 1957)

Channels."[7] He pointed out that only 100 years had passed since the appearance of the earliest of Magendie's epoch making publications in which attention was drawn to the physiologic importance of the peculiar watery medium which bathed the central nervous system. Cushing then went on to review the current knowledge regarding the spinal fluid's origin and the course of the cerebrospinal fluid. It was already known that the cerebrospinal fluid was in continual movement and in a definite direction fur thermore it traveled through a highly special pathway in a fashion which served the purpose of lymphatic drainage, since lymphatic vessels as such were not present in the brain (Fig. 264)

In 1911 Dandy[8] had devised a method of producing experimental hydrocephalus by occluding the aqueduct of Sylvius and of determining the site of the block by an injection of phenolsulfonphthalein. It was subsequently found that when one foramen of Monro was occluded a unilateral hydrocephalus resulted yet if the choroid plexus in that lateral ventricle was removed coin cidentally the ventricle remained collapsed. This proved beyond doubt that the cerebro-

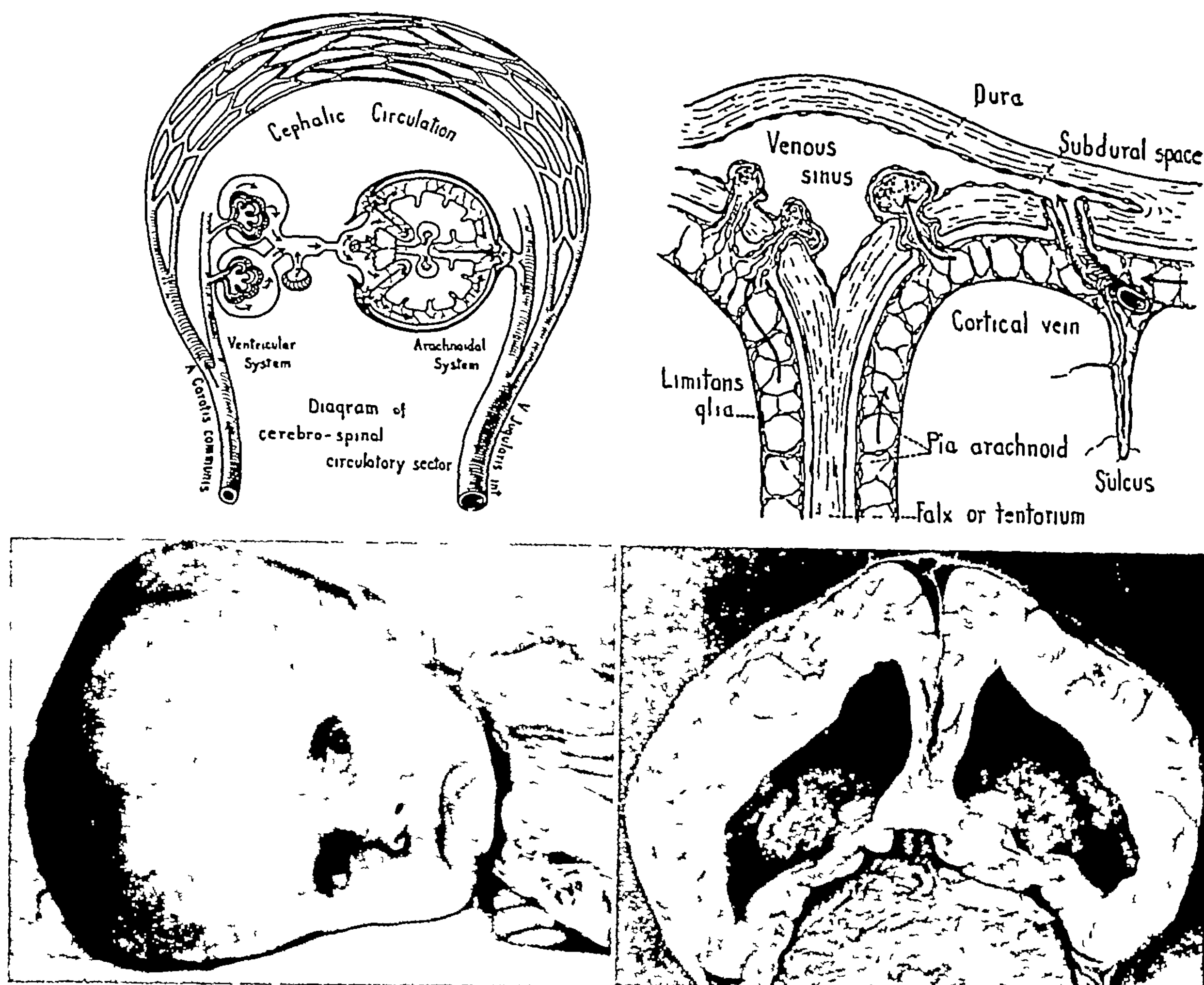


Fig 264 Circulation of the cerebrospinal fluid Above are shown the processes of formation and absorption of cerebrospinal fluid It is formed by the choroid plexuses and absorbed in the arachnoidal system over the brain and spinal cord (From Cushing, H *Studies in Intracranial Physiology and Surgery* London, Oxford University Press, 1926) Below is shown a child with the characteristic physical changes of hydrocephalus (Courtesy of Dr Orlando J Andy) and also bilateral hypertrophy of the choroid plexuses (From Davis, L E A physio-pathological study of the choroid plexus with the report of a case of villous hypertrophy J M Research, **44**· 521, 1924)

spinal fluid was secreted by the choroid plexuses Previously Cushing had observed fluid freely exuding from a choroid plexus in a patient who had a unilateral hydrocephalus due to a cystic intraventricular tumor arising near and occluding the right foramen of Monro When a clip was placed on the entering choroidal artery, however, the choroid plexus blanched and the secretion apparently ceased

The cerebrospinal fluid passes from the lateral ventricle, to the foramen of Monro, into the third ventricle, through the aqueduct of Sylvius to the fourth ventricle, out into the subarachnoid space through the foramen of Luschka and the foramen of Magendie It is absorbed chiefly by the arachnoid villi into the dural sinuses and the spinal veins Roughly four-fifths of the fluid is absorbed by way of the cerebral arachnoid villi and most of the rest by way of the spinal villi (Fig 264)

Factors which affect cerebrospinal fluid flow and pressure *Hydrocephalus resulting from obstruction* We have previously alluded to the studies of Dandy, among others, who demonstrated that hydrocephalus is usually the result of a blockage of the outflow of the cerebrospinal fluid from the ventricular choroid plexuses, where it is formed, through the roof of the fourth ventricle into the subarachnoid spaces Ac-

tually, very rarely hydrocephalus may result from an excessive rate of formation of cerebrospinal fluid, though this is of no particular clinical significance In Figure 264 is shown a case cited by Cushing[7] which had been reported by Davis [10] It was thought that huge bilateral but symmetrical hypertrophy of the choroid plexus had resulted in the formation of fluid at a rate that was in excess of the capacity of the subarachnoid villi to reabsorb

Nevertheless, hydrocephalus usually is caused by actual blockage of the flow of the cerebrospinal fluid. *Internal hydrocephalus is the term applied to a blockage of the fluid* before it has left the ventricles This could occur by blockage of either foramen of Monro which would produce a unilateral *hydrocephalus in the lateral ventricle*, or the blockage could occur in the aqueduct of Sylvius, which would produce dilatation of the ventricular system proximal to this or *it could occur due to sclerosis in the roof or* lateral exits of the fourth ventricle. *External hydrocephalus* on the other hand, is the term applied to the extraventricular hydrocephalus which results from a blockage of the free flow of the fluid through the subarachnoid space and thus diminishes the total number of arachnoid villi available for absorption Inflammatory changes in the leptomeninges may occlude the arachnoid villi and in this way prevent absorption In fact, Weed[23] showed in 1919 that a chronic high grade hydrocephalus could be produced experimentally by the subarachnoid injection of lamp black which served to occlude the villi

Every neurosurgical service has its share of unfortunate children with hydrocephalus, and large numbers of essentially unsuccessful operative procedures have been attempted in an effort to permit successful chronic drainage and decompression

EFFECT OF INTRAVENOUS THERAPY ON CEREBROSPINAL FLUID PRESSURE In 1919 Weed and McKibben[24] *demonstrated that prompt* changes in brain volume followed the intravenous injection of hypertonic and hypotonic fluids. The use of hypertonic solutions was promptly adopted as a means of lowering intracranial tension, and it was noted that certain patients who were in a deep stupor, even with Cheyne-Stokes respiration, could be brought back to consciousness after such treatment However, this and related measures have ultimately proved to be of limited value In brief, the intravenous injection of an hypotonic solution may result in a marked and prolonged rise in cerebrospinal fluid pressure In contrast, if an hypertonic solution is given there is a temporary lowering of the intracranial pressure The *solution most commonly used for this is* 50 per cent sucrose given in the amount of from 50 to 100 cc intravenously It is possible also to dehydrate the individual by giving *small doses of magnesium sulfate* by mouth each day

Incidentally in the course of his experiences in the management of hydrocephalus *in children Cushing observed that electro*lyte imbalance might lead to intestinal intussusception in youngsters This is a major cause of death in uremic dogs

Mechanics of Increased Pressure

To appreciate the effect which changes in increased intracranial pressure may have upon *the* brain, it *is well* to bear in mind *that* the brain and its coverings are encased in a tight bony box. Since the brain itself contains large amounts of incompressible water there are definite limits to which the intracranial pressure can rise without causing irreversible damage to nerve cells

When the intracranial pressure rises—whether due to hemorrhage and clot edema, tumor, abscess or depressed fracture—the cerebrospinal fluid is forced out along the sheaths of the cranial nerves and if this process continues with sufficient severity, permanent brain cell damage will occur As we know, the increase in intracranial pressure results in edema of the optic disc

For a time the increased pressure in the arteries relative to that in the veins will continue to bring in blood whose exit through

the veins is partially limited by the pressure upon the veins Thus, an increase in the intracranial pressure usually results in displacement of some of the cerebral fluid The blood vessels may be compressed and the surface of the gyri flattened Finally, when all possible intracranial space has been taken, the pressure is exerted on the contents of the posterior fossa of the skull and the cerebellar peduncles are gradually herniated downward into the foramen magnum This may so obstruct the foramen magnum that the spinal fluid can no longer escape into the subarachnoid space of the spinal canal, where a portion of the normal absorption of this fluid occurs It is probable that as the intracranial pressure increases, the pressure of the confining foramen magnum upon vital medullary centers results in respiratory paralysis due to anemia of the respiratory center *Respiratory failure usually precedes failure of the heart*

Signs and Symptoms of Acutely Increased Intracranial Pressure

The surgeon most frequently encounters acutely increased intracranial pressure in connection with traumatic accidents There is the history of head injury, with or without loss of consciousness However, patients who sustain serious head injury often do lose consciousness for hours, days, weeks, or even months It is customary to consider the pathophysiology of acute head injury under the categories of concussion, contusion, and compression, though in the given case these are apt to merge and to be of little clinical aid In brief, concussion represents the circumstance in which one is momentarily "knocked out," as by a blow to the jaw Serious brain damage is not present In contusion, however, and in compression of the brain, there may be extensive tissue edema, hemorrhage, and laceration

As intracranial pressure rises due to gross hematoma or diffuse edema and hemorrhage, the *blood pressure* rises but the *pulse rate* and the *respiratory rate* decline If the contents of the skull continue to swell, respiration may be of the Cheyne-Stokes type before it fails The initial rise in blood pressure is followed by a fall in blood pressure and an increase in pulse rate—signs which often herald the approach of death Finally, a marked increase in the body temperature, usually without sweating, is observed Most of these alterations in vital signs are due to terminal ischemia of the medullary center Thus, *the early warning signs of brain compression are a rise in blood pressure, a slowing of the pulse, a deepening of unconsciousness, and slowing or irregularity of respiration*

Signs and Symptoms of Chronically Increased Intracranial Pressure[27]

In the more gradually produced increased intracranial pressure (and even in the acute) any or all of the following signs and symptoms of increased intracranial pressure may be noted and all should be viewed with insight when they are encountered

Headache This is apt to be severe and is rather constant It is likely to be made worse by any movement which increases intracranial tension, such as straining at stool, rising, bending over, coughing, or sneezing

Vomiting This may be of the "projectile" type and is usually not preceded by nausea

Choked disc This visible sign may be associated with subjective evidence of diminished vision and objective evidence of visual field defects

Stupor and, later, unconsciousness This is due to an increase in intracranial pressure causing anoxemia of vital centers

Blood pressure and pulse As noted with acutely increased intracranial pressure in trauma, a rise in blood pressure and a slow bounding pulse associated with slowed respiration is a sign of increased intracranial pressure With a further increase in intracranial pressure the blood pressure will fall the pulse will become rapid, and respiration will eventually cease

Miscellaneous other signs are vertigo,

mental dullness and deterioration, convulsions and strabismus.

Focal Signs of Increased Intracranial Pressure[19]

Mass lesions produce symptoms by increasing intracranial pressure and by affecting particular areas of the brain.

Frontal lobe Lesions of the frontal lobe are insidious in onset and are usually manifested first in *personality changes* Diminished mental capacity and attention to surroundings may accompany a loss of care in personal tidiness Hemiparesis will not be present unless there is encroachment upon the motor cortex as the mass enlarges Convulsions may then occur and speech disturbances are not uncommon

Motor cortex Lesions of the motor cortex cause convulsions on the side of the body opposite that of the lesion If relief is not provided, contralateral hemiparesis and, eventually, complete paralysis may develop

Parietal lobe Since this lobe is the seat of sensation and stereognosis, the following signs may be observed Convulsive seizures may be preceded by a sensation of tingling or numbness with associated change in sensory appreciation, astereognosis or the inability to determine size shape weight and texture of objects may be lost even though tactile and touch perception may be intact.

Temporal lobe Lesions of this lobe may be accompanied by hallucinations of smell The odor (not noted by the attendant) is usually disagreeable and may be associated with a smacking of the lips Dreamlike states may be present and an occasional auditory hallucination and difficulty in understanding spoken words may be observed though sound is appreciated Various speech disturbances, or types of aphasia are seen If the motor cortex is impinged upon varying degrees of hemiparesis of the opposite side of the body may be observed.

Occipital lobe As the occipital lobe has an important association with visual function, visual hallucinations may precede generalized convulsions

The cerebellum The signs and symptoms of cerebellar lesions are not readily overlooked An ataxic gait and station are characteristic the patient walks with a broad base feet wide apart, and with staggering There are other lesions which can produce such a gait but a cerebellar lesion must always be considered. An increase in intracranial pressure, with severe and continued headache and early visual disturbances, is common Vomiting of the projectile type is frequently observed A marked nystagmus is often associated with vertigo tinnitus and occasionally with fainting. Adiadochokinesis is a characteristic finding of lesions of the cerebellum and posterior fossa Not infrequently the patient will hold his head so that the occiput is toward the side of the lesion and patients have a tendency to fall to the side of the lesion Past pointing is likely

Pituitary tumors The changes which occur in the presence of pituitary tumors have much to do with the endocrine system and were outlined in that section (p 533) The important facts to be noted in this particular discussion are that a pituitary tumor of increasing size causes pressure on the surrounding structures and may be accompanied by a marked loss in vision as the lesion progresses These pressure changes usually arise from the eosinophilic chromophobe or mixed tumors since the basophilic adenomas are typically very small

The usual findings in the presence of pituitary enlargement are as follows Headache is an early symptom Photophobia may be associated with marked visual disturbances consisting particularly of a bitemporal hemianopsia. That is the fibers crossing through the optic chiasm are damaged so that the individual is not able to see normally in the temporal fields. Actual atrophy of the optic nerves may occur and eventually almost complete blindness may be noted Roentgen examination frequently shows enlargement of the sella turcica.

The Care of Acute Head Injuries[30]

Numerous physiologic requirements are involved in the early management of head trauma [23] Certain of these may be illustrated by outlining the treatment of these injuries

1 *Treatment of shock* Regardless of the type of head injury, shock must be treated immediately, before more definitive other therapy is undertaken The principles of the management of shock are discussed elsewhere

2 *State of consciousness* If the patient is not unconscious on admission to the hospital, he should be watched very carefully that he does not become so If he does become so, certain other measures listed below are indicated A careful neurologic examination is recorded at the time of initial evaluation

3 *Chronologic clinical record* A careful clinical record is kept of the pulse, respiratory rate, blood pressure, and changes in neurologic signs

4 *Scalp laceration* Since a scalp laceration may be associated with a much more serious underlying injury to the skull or brain, it is advisable simply to cover the defect with a sterile dressing until the patient's shock and other pathology have been evaluated Following the more urgent measures, the head can be shaved and the scalp laceration cleansed and sutured, after the skull has been carefully examined with the gloved finger for a fracture Skull roentgenograms should always be taken where there is any suspicion of a possible fracture

5 *Bleeding or discharge of cerebrospinal fluid from ears or nose* This generally indicates a fracture at the base of the skull which is permitting the fluid and blood to come to the outside Such fractures are usually serious If other pathologic findings are not present, the chief objective in therapy is to prevent the development of meningitis The use of heavy doses of antibiotics is indicated The nose should not be manipulated or swabbed or sprayed, and the patient should be cautioned against sneezing In most cases the discharge ceases within a few days and no further difficulty arises The general care of drainage from the external auditory canal is similar to that for the nose. Where possible, the patient should lie with the injured ear downward on a large sterilized gauze pad

6 *Management of cerebral edema* There is much disagreement among neurosurgeons regarding the value of the various methods other than surgery that may be used (dehydration, intravenous injection of hypertonic solutions, or spinal tap) Hypothermia may be helpful

7 *The position of the patient* Most neurosurgeons feel that the patient should be kept flat in bed for some days following a period of unconsciousness, and for much longer periods if serious brain damage has been present The chief reasons for doing this are to minimize alterations in intracranial pressure and to diminish the likelihood of posttraumatic "neuroses" Actually, the so-called neurosis may consist of dizziness and headaches that are quite real During recent years there has been the tendency to allow patients to be ambulatory somewhat earlier following simple postconcussion unconsciousness that is not associated with demonstrable brain injury

8 *Bladder care* Patients with increased intracranial pressure may become incontinent of urine before unconsciousness occurs, and of course they will have to be catheterized if they are unconscious To diminish the excoriation of the skin by urinary incontinence with the development of bed sores, to maintain bladder tone, and to diminish the likelihood of bladder infection, some method of evacuation of the bladder with frequent irrigation is commonly used

9 *The relief of pain* The application of ice bags to the head will frequently markedly diminish headache The routine use of morphine is to be discouraged because it diminishes respiration, which is already reduced, and because in addition it constricts the pupils and precludes the use of pupil examinations for the localization of the lesion, such as a dilating pupil on the side of

the injury would do When *morphine* must be used it should be used with caution, and frequent small doses are to be preferred to large doses given less frequently Codeine may be used or, even better barbiturates may suffice. In addition to stimulating respiration caffeine sodium benzoate may also lower the intracranial pressure somewhat.

10 *Control of hyperthermia* The use of multiple ice bags may be sufficient to maintain the temperature below 104° F Cooling is further facilitated if the skin is moistened and multiple electric fans blown over it However, at times even these measures, combined with the use of aspirin, may be inadequate. Under such circumstances an ice water enema may be given and repeated as often as necessary From 300 to 500 cc of fluid may be administered as an enema and withdrawn after from 15 to 20 minutes. One of the various types of cooling apparatus used in producing clinical hypothermia may also be employed.

11 *Tracheostomy* This should be done if indicated.

12. *Operative intervention* If a mass lesion is present and operable, surgical intervention will prove far superior to the conservative measures listed above

Electroencephalography

It would be incomplete to have alluded to intracranial mass lesions and injuries without mentioning the electroencephalogram (EEG) In 1929 Hans Berger[3] reported the surprising observation that tracings could be made of the electrical activity of the brain through the unopened skull Since then this discipline has advanced steadily A person expert in reading and interpreting the EEG is essential The EEG is particularly helpful in the diagnosis localization and prognosis of lesions producing various forms of epilepsy It is helpful also in the diagnosis and localization of brain tumors, and in localizing residual scar following traumatic injury (Fig. 265) There is a fairly good correlation between the recovery of the damaged tissues and the return of the EEG to normal As pointed out by Gibbs[13] the specific nature of the abnormalities which produce the electroencephalographic changes are usually not indicated by an EEG That is the EEG abnormalities are much the same whether produced by trauma vascular pathology, infection, or neoplastic disease. Nevertheless the variations which are observed may lead one to suspect that a particular type of lesion is developing. This is especially apparent if one can compare the changes in the EEG that have appeared over a period of days weeks, or months.

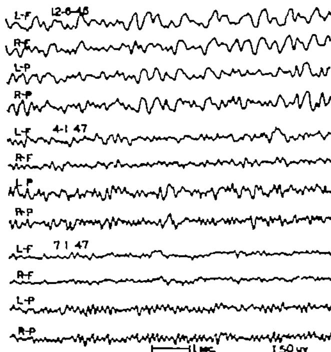


Fig 265 An electroencephalogram following cerebral contusion Electroencephalographic tracings (four channels) of a 9-year-old boy following cerebral contusion The upper four tracings, taken on the day of injury December 6 1946 show diffuse irregular slow activity of 2- to 4-per-second waves The second series taken on April 1 1947 still show moderately slow wave activity but it is approaching normal The lower four tracings, taken July 1 1947 show that the electrical activity has nearly returned to normal 8-per-second waves. This boy was unconscious for 4 days and made a satisfactory recovery The correlation between the brain wave tracings and the clinical course is close in this case (From Rand C W In *Textbook of Surgery* Ed 5 edited by F Christopher Philadelphia W B Saunders Company 1949)

A high degree of asymmetry between the left and right halves of the brain, even though both show normal patterns, is thor-

oughly reliable EEG evidence of the lateralized injury, if a lesion is present, it is usually on the side of the reduced voltage Nevertheless, the EEG may be entirely normal in the presence of serious brain damage Thus, the negative EEG does not rule out disease, but positive EEG findings are of important confirmatory value A particularly important application of the EEG lies in the value of a positive finding in patients who have seizures which may or may not rest upon an organic basis The finding of abnormal activity would establish the organic nature of the disease, whereas the patient might otherwise be considered to be neurotic On the other hand, again, a normal electroencephalogram would not exclude organic disease



Fig 266 Café au lait pigmentation of von Recklinghausen's neurofibromatosis This disease may affect virtually any organ Uremia is not rare, due to ureteral obstruction (Courtesy of Dr Temple Ainsworth)

Neurofibromatosis (von Recklinghausen's Disease, Fig. 266)

In closing, mere mention will be made of tumors of nerve tissue In the brain the symptoms and signs of local pressure or of a generalized increase in intracranial pressure usually prompt the individual to consult a physician The pheochromocytoma

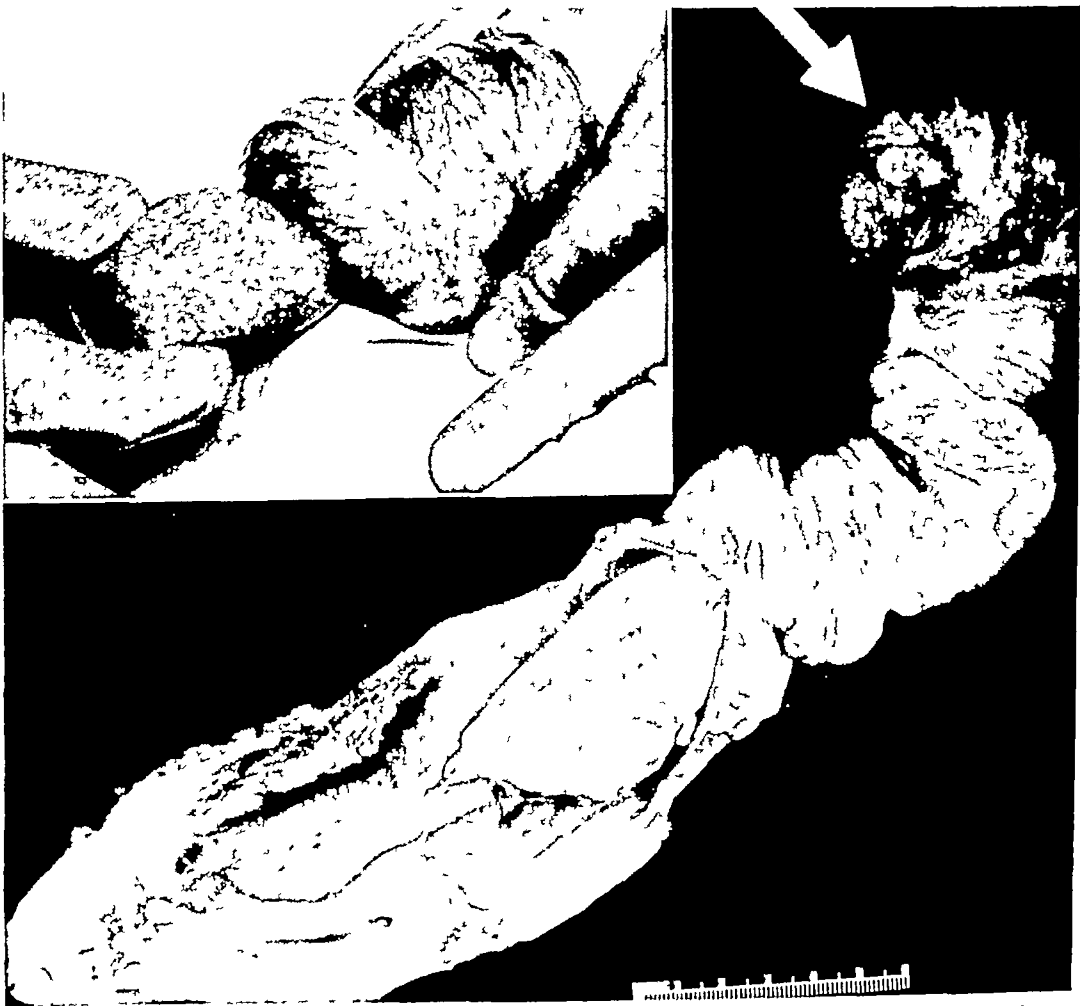


Fig 267 Intussusception due to neurogenic polyp The patient had von Recklinghausen's neurofibromatosis, and had numerous tumors elsewhere

and neurofibromatosis are closely related. Finally, nervous tissue tumors can produce dysfunction in any organ or region of the body including intussusception (Fig 267)

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Chapter 20

Infancy Poses Special Problems

The very young often confront the surgeon with special problems in anatomy, pathology, physiology and technic that are largely absent in older persons. Therefore while one would not wish to imply that the physiology of the infant is qualitatively very much different from that of the adult, there are certain quantitative differences which are of importance to surgeons. Moreover, it is in the infant that congenital defects are usually discovered and corrected and we may quite properly concern ourselves briefly with the pathogenesis of developmental defects. The following areas will be considered: the pathogenesis of developmental defects, the altered physiology found in newborn and premature babies and the metabolic response of infants to anesthesia and operation.

Pathogenesis of Developmental Defects

Surgical considerations in the young must begin even before birth, for the surgery of children has to do frequently with the correction of developmental defects. It has become highly important to distinguish more precisely between the defects that are hereditary or genetically transmitted and those which are merely congenital (present at birth). The reason for this is that, more and more congenital defects that were previously thought due to deranged chromosomes and genes are now being found to be due to maternal disease during pregnancy. Accordingly the popular notion that most congenital defects are inevitable because of genetic aberrations must be searchingly reappraised. There can be no question but that many developmental defects will be shown to be preventable.

Historical Notes

That maternal disease could produce defects in the fetus was noted by Jonathan Hutchinson through his studies of congenital syphilis. However, the broad significance of this observation, relative to the prevention of developmental defects, was long ignored by the medical profession. In 1924 Talbot[13] stated his belief that most congenital malformations that were the result of lack of embryonic development were not hereditary defects but were acquired *in utero*. He considered that these defects were due to placental injury during the early period of gestation. Talbot described 20 consecutive cases of deformed infants in which there was evidence of placental damage near the base of the cord; 6 of the babies were anencephalic.

In 1941 Gregg[8] pointed out the relationship which exists between the development of congenital cataract and other deformities and the occurrence of German measles (rubella) in the mother during pregnancy. In 1952 Olim and Turner[9] reported a patient with tetralogy of Fallot who twice delivered at 6 months gestation an anencephalic infant; following a Blalock operation the mother delivered a normal infant at term.

Experimental Studies

In 1877 Camille Dareste[3] reported the artificial production of monstrosities including anencephaly in the chick embryo, as a result of thermal insults to the embryo-

nated egg However, it is only in recent years, through the experimental studies of Ingalls[7] and others, that the epidemiology of congenital defects has surged forward Noting that such commonplace defects as those associated with mongolism often had been associated with a possible etiologic episode during pregnancy, especially in conditions leading to anoxemia, Ingalls and others embarked upon a series of controlled studies They decided upon oxygen lack as one stimulus to use, and it was soon found that multiple and different anomalies could be produced at will, depending upon the timing of the *maternal stress* induced by the anoxia in mice For example, gross defects of the skull and of the brain were produced experimentally as localized manifestations of oxygen lack on the ninth day of gestation

With such anoxia (usually produced by means of atmospheric pressures simulating altitudes of 25,000 to 30,000 ft—as atop Mt Everest) the *timing* of maternal stress in pregnancy and its *intensity* can be varied at will The mother can be subjected to anoxia on any desired day, and the timing in gestation and the degree of stress used can profoundly influence the type and number of congenital defects to be found in the young Using stress anoxia upon fish eggs, Ingalls and co-workers were able to induce embryonic deformity as early as the 16-cell stage

It is not necessary to list the variety of congenital defects that can be produced at will under controlled experimental conditions The fact is, most of the congenital defects with which the pediatric surgeon is so commonly engaged have already been produced experimentally According to Ingalls, "*The evidence is overwhelming that many, if not most, anomalous children have survived a temporary intrauterine stress*" (Fig 268)

Types of Teratogenic Agents

In addition to anoxia, certain vitamin deficiencies, cortisone, trypan blue dye, and ionizing radiation have been used to produce anomalies The development of mutations among exposed Hiroshima residents has not appeared However, brachycephaly and mental retardation occurred in 11 babies of mothers pregnant and standing within three-quarters of a mile (1,200 m) of the hypocenter at the time of the explosion, such defects were not found among the progeny of mothers at greater distances

Prevention of Anomalies[7]

It has been suggested that proper attention to teratogenic factors already known

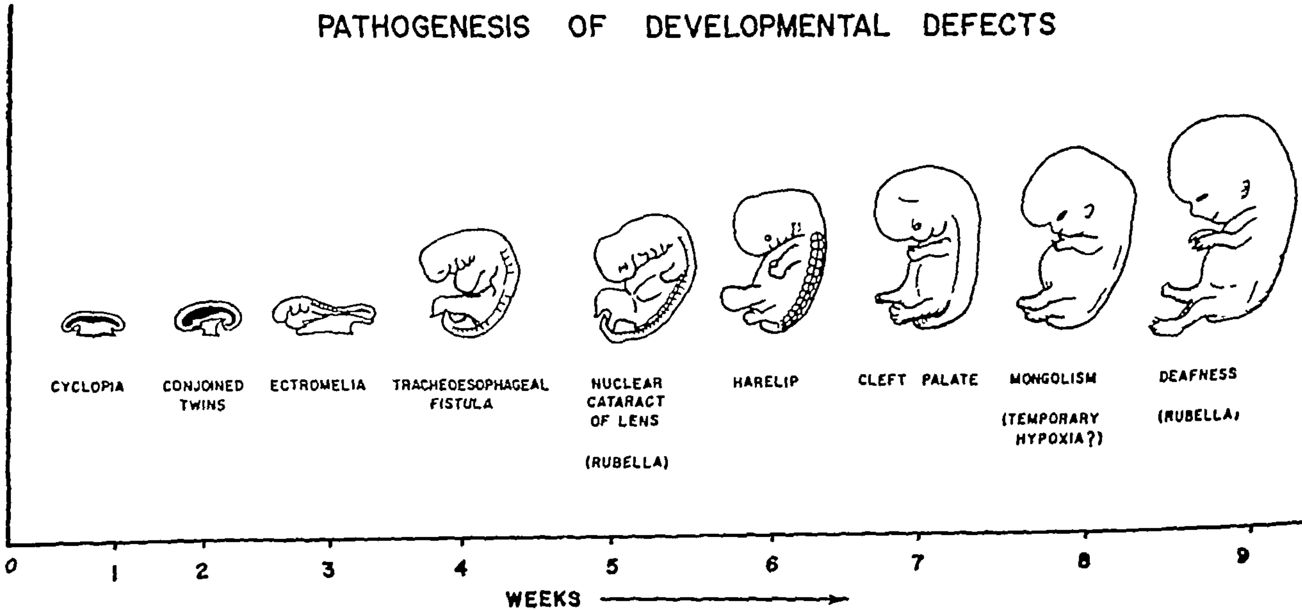


Fig 268 The evidence is steadily increasing that many or most developmental defects are due to stress imposed upon the fetus at the time the particular organ involved was being formed Thus, many congenital defects may prove to be preventable[7]

TABLE 24 SOME REPRESENTATIVE CONGENITAL ANOMALIES

A. Head and neck
 1 Congenital hydrocephalus
 2 Hare lip cleft palate or both
 3 Microtia (small ears)
 4 Thyroglossal duct cyst
 5 Cystic hygroma
 6 Branchial cleft cyst
B Lungs and trachea
 1 Congenital arteriovenous fistula
 2. Congenital cysts
 3 Tracheo-esophageal fistula
 4 Agenesis of lung
 5 Sequestration of lobe
 6. Anomalous vessels and bronchi
C Heart and great vessels (incomplete list)
 1 Tetralogy of Fallot
 2 Transposition of aorta and pulmonary artery
 3 Transposition of great veins
 4 Septal defects
 5 Coarctation of aorta
 6 *Patent ductus arteriosus*
D Alimentary tract
 1 Esophagus
  (a) Atresia (with or without fistula)
  (b) Reduplication
 2 Diaphragmatic hernia
 3. Stomach
  (a) Hypertrophic pyloric stenosis
 4 Small intestine
  (a) Duodenum
   (1) Atresia or stenosis
   (2) Annular pancreas
   (3) Undescended cecum with duodenal compression
  (b) Jejunum and ileum
   (1) Atresia
   (2) Duplication
   (3) Cysts
   (4) Malrotation
   (5) Meckel s diverticulum or persistence of vitelline duct
   (6) Meconium ileus (deficiency of pancreatic enzymes)
  (c) Colon rectum and anus
   (1) Congenital megacolon
   (2) Imperforate anus
   (3) Rectovaginal rectovesical or recto-urethral fistulas
E. Genitourinary tract
 1 Kidneys
  (a) Horseshoe kidney
  (b) Cystic disease
 2. Ureters
  (a) Congenital mega ureter
  (b) Double ureter

TABLE 24 —*Cont d*

 3 Bladder
  (a) Exstrophy
  (b) Patent urachus
 4 Urethra
  (a) Various bands septa or valves
 5 Penis
  (a) Hypospadias
  (b) Hermaphrodism
 6 Scrotum
  (a) Undescended testicle
F Liver
 1 Atresia of bile ducts
G Abdominal wall
 1 *Omphalocele*
 2 Hernias
  (a) Umbilical
  (b) Inguinal
H Skeleton (a representative few)
 1 Various skull anomalies
 2 Missing or supernumerary parts of extremities
 3 Congenital dislocation of the hip
 4 Pectus excavatum

will reduce the incidence of anomalies in the foreseeable future Among such preventive measures for the mother are

1 Allow small children to acquire rubella and perhaps mumps and chicken pox naturally *Protect against pertussis* Develop vaccine to prevent influenza during pregnancy Treat syphilis promptly

2 Avoid anemia and hypothyroidism *Correct, insofar as possible* organic heart disease systemic hypertension retroflexion, and tumors of the uterus.

3 Control diabetes carefully Avoid maternal anoxia at operation or dentistry Avoid radiation and marked dietary deficiencies Avoid cortisone therapy

4. Older women have a higher incidence of anomalous offspring and their general health should be meticulously maintained.

Some Congenital Defects of Surgical Importance

In order to indicate the extent to which congenital defects occasion surgery in infants a few such defects are listed in Table 24 and in Figures 269–274.



Fig 269 Patient F W, 5 days after division of patent ductus This very common congenital lesion is well tolerated for a number of years by most patients In some, however, pulmonary hypertension of such magnitude develops as to preclude successful division of the ductus



Fig 270 Sequestrated lung The bronchus of the collapsed, solid lung held by the lung clamp connected with the esophagus only, not with the tracheobronchial tree Its arterial blood supply was derived from the aorta at a level just below the diaphragm (From St Raymond, A H, Jr, Hardy, J D, and Robbins, S G Lower accessory lung communicating with the esophagus and associated with congenital diaphragmatic hernia J Thoracic Surg, **31.** 354, 1956)

In conclusion, human embryogenesis represents an almost unbelievably complex and delicate process, any one of whose myriad components may be arrested at a given time Whenever such an arrest in development of a part occurs, even if temporary, the result



Fig 271 Biliary tract obstruction Thought to have atresia of the extrahepatic biliary tract, this infant proved instead to have obstruction of the terminal common duct by inspissated bile which was flushed through Unfortunately, it is bile duct atresia that is more commonly encountered in the presence of intractable jaundice following birth, and in the majority of patients little can be done

of this arrest appears in the offspring as a deformity

Some Hemodynamic Changes that Occur in Fetal Circulation at Birth

In Figure 127 it may be seen that several very important changes must occur at birth The ligation of the umbilical cord stops the circuit of blood through the hypogastric arteries to the placenta The foramen ovale closes functionally because of the increased pressure in the left atrium The ductus arteriosus usually closes quite promptly The valves of the inferior vena cava atrophy, and the pulmonary circulation reaches the normal volume

The timing and the mechanism of the closure of the ductus arteriosus has been rather obscure However, recently some fascinating work performed in the Nuffield Institute in England has shed considerable light on this question [10] The experimental

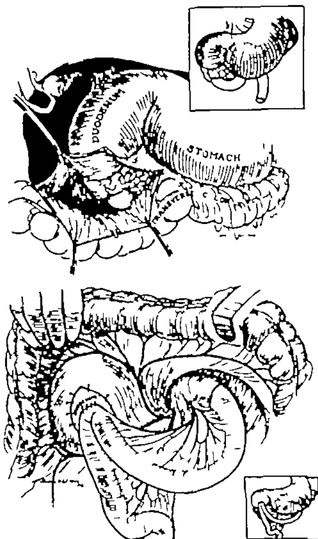


Fig 272 Annular pancreas and its management To avoid possible common duct injury and pancreatic fistula, it is usually better not to try to resect the obstructing pancreatic annulus but to perform duodenojejunostomy (From WILSON H AND BUSHART J H Annular pancreas producing duodenal obstruction Ann Surg 137: 818 1953)



Fig 273 Patent urachus—the urachus is derived from the allantois (From BENTON B F, LANGFORD H G AND HARDY J D Patent urachus. Am. J Surg 88: 513 1954)

work was performed using cinema roentgenography in the fetal and 2-day-old lamb After establishing that the adult type circulation existed in the 2 day-old animal the investigators delivered lambs by cesarean section, with placental circulation remaining intact. A nosebag was placed over the fetus to prevent respiration and the circulatory pathway through the heart, lungs and aorta was followed by the injection of radiopaque medium *Blood left the right* ventricle through the pulmonary trunk and entered the ductus arteriosus. Mixing and turbulence of the aortic and pulmonic streams at the end of this shunt indicated patency of this bypass In contrast to that seen in the postnatal state, filling of the pulmonary artery was slow most of the pulmonary artery blood being shunted through the ductus into the aorta. However, *within minutes after tying the cord and the beginning of pulmonary ventilation, the ductus arteriosus closed* Whereas previous to pulmonary ventilation there was almost no pulmonary flow, one cardiac ejection now filled the lungs The pulmonary blood volume rose literally with the first breath, and unless pulmonary ventilation occurred these flow alterations were not observed

Blood pressure changes were also followed in the fetal lamb With the onset of respiration both pulmonary and systemic systolic pressures fell to about 40 mm. Hg When the umbilical cord was tied there was some recovery of systemic pressure, but the most rapid recovery observed took place about 15 minutes after the acute pulmonary changes were over Similar pressure trends were observed in a series of human newborns *studied by the skin flush method*

Thus, the suggestion that functional closure of the patent ductus arteriosus need be due to fibrosis is no longer tenable on the basis of the data for sheep given above.



Fig 274 Meckel's diverticulum at surgery This congenital defect results from the persistence in varying degrees of the vitello-intestinal duct The diverticulum shown above was quite contractile, and it alternately shortened and lengthened as it was handled The base was cross-clamped, the diverticulum was excised, and the stump was inverted

While fibrosis surely does occur eventually, functional closure by contractile elements and longitudinal stress would appear to be a tenable explanation that could account for immediate cessation of ductus flow upon expansion of the lungs Of course, the angiocardiography would not so readily reveal flow from aorta to pulmonary artery, due to pressure alterations, and this reversal of the direction of flow (from that of fetal life) may persist somewhat longer

Altered Physiology Found in Newborn and Premature Babies

The physiology of the newborn infant was reviewed by Smith[12] in monograph form in 1951, and this source has been drawn upon freely in the following discussion

Respiratory Problems

The question of whether or not respiratory movements occur *in utero* would appear to have been settled in the affirmative However, this fetal activity has little relationship to the respiratory effort required to sustain life once the cord is tied Under normal circumstances, when the respiratory centers have not been depressed by anesthesia, the human infant seemingly can begin to breathe simply by the reflex response to the stimuli of exposure at birth Thereafter, breathing is more or less rhythmical if the infant is normal

When surgery must be performed upon premature and full-term infants, the efficiency of respiration becomes a matter of great practical importance, and it has seemed to us that more neonatal surgical deaths are due to respiratory complications than to any other single cause

It has been pointed out that the respiratory movements of the newborn are almost entirely diaphragmatic If movement of the diaphragm is interfered with by abdominal distention or diaphragmatic hernia, the infant—and especially the premature infant—is in a most critical state Even at best, the respiratory efforts of the premature are often shallow, rapid, and irregular, a poor starting point when surgery must be done Hence, extreme care must be exercised during anesthesia to minimize depression of respiration and periods of relative anoxia

Circulatory Problems

The entire homeostatic mechanism of the premature and, to a lesser extent, of the full-term infant is more fragile than that of the older subject The circulatory system is no exception

First the total blood volume of the premature is very small, and even small losses at surgery are highly important. For example, suppose that the total blood volume of a 4-lb (1 8-kg.) premature is approximately 10 per cent of body weight, or 180 cc, obviously, blood loss must be minimized and it must be adequately but meticulously replaced Overtransfusion can be as disastrous as undertransfusion.

Coagulation defects are relatively common in the newborn and particularly in prematures. Many of the protective physiologic mechanisms of which blood clotting is an important one, are not yet fully developed in infants

Body temperature regulation is always a problem in prematures, for several reasons (1) metabolism and heat production are deficient, (2) body heat regulating centers with their peripheral afferents and efferents are less rugged and (3) subcutaneous fat (insulation) is at a minimum Therefore unless the ambient temperature is carefully controlled the body temperature of the small infant may vary widely with changes in room temperature This is especially true of prematures since their body surface area exposed for cooling or heating is relatively enormous when compared with that of the adult. Specifically the weight of a full term infant is approximately 5 per cent of that of an average adult while his body surface area is 15 per cent of that of the adult

Vasomotor stability is much less sturdy in the very young, and for this reason they are less able to withstand conditions which would not seriously handicap the circulatory apparatus of the adult.

The *systemic systolic blood pressure* in the umbilical artery increases from 33/? in the 5-month fetus to 70/35 in the 7 month fetus to 80/46 in the full term fetus.[15] At the neonatal age of 10 days this value usually lies between 90 and 100 mm Hg In prematures the blood pressure normally ranges from 60 to 80 mm. Hg.

It is manifest that a truly convenient method for accurate intermittent measurement of the blood pressure during operation upon all infants is urgently needed The anesthesiologist and the surgeon will otherwise have little inkling of the status of the blood pressure of the diminutive patient it is merely known, by auscultation that the heart is still beating and, by observation, that any shock that might exist has not yet halted respiratory effort. Since cardiorespiratory stability is admittedly precarious in the very young it is especially important that undue stress upon the cardiovascular system be avoided

The heart rate declines at birth from the more rapid fetal rates to about 120 to 130 per minute however, there is much variability and rates of from 90 to 180 are frequently observed in normal infants The slightest exertion may cause marked tachycardia in many infants

The Alimentary Tract

The gastrointestinal tract of the newborn infant has the normal complement of secretory and absorbing mechanisms, but the supporting musculature is less well developed Thus, food absorption proceeds satisfactorily but distention readily occurs The enzymic activity of the upper gastrointestinal tract is adequate for the digestion of most simple foods Although the pH of the gastric contents is about 7 0 immediately after birth there occurs within a few hours a sharp relatively transient and unexplained increase in activity

The *meconium* consists of enzymes residue from swallowed amniotic fluid desquamated cells from the mucosa and traces of blood from unrecognized sources About 60 to 200 gm. are present in the bowel at birth Some meconium is usually passed within the first 10 hours postnatally, and normally all of it has been evacuated by the fourth day The meconium in the alimentary tract while sterile at birth, often contains bacteria 5 hours later and after 24 hours it always does so

The *Farber test* for patency of the alimentary tract where atresia is suspected at

birth, consists of demonstrating swallowed epithelial cells in the center of the meconium stool.[4]

In general, the digestive tract of the newborn is adequately fitted to receive the usual food offerings.

Renal Function

Much has been written regarding renal functional capacities in premature and full-term infants, not a negligible amount of which has conflicted. The reason for this surely lies, in part, in the technical difficulties inherent in the study of a sufficient number of subjects to achieve statistically reliable data. Therefore, the following comment will be restricted to generalizations that are fairly well agreed upon.

As with various other organs or systems, the kidneys do not reach anatomic maturity until about the thirty-fifth week after conception—whether or not all of this period is spent *in utero*.[12] Therefore, while the kidney of the infant is able to cope with ordinary requirements, it is ill prepared to cope with either excess or deficit of fluid, especially of salt-containing fluid. That is, the infant kidney can neither efficiently conserve sodium, if needed, nor can it readily excrete sodium when administered. Hence, the use of saline solution in the very young promptly results in edema in many instances. Since babies are born with an excess of water that amounts to from 5 to 10 per cent of body weight and which must be excreted during the first day or so of life, the immediate fluid requirements at birth are small. Water intake may properly be restricted until the second to the third day, when the usual milk intake of infancy is established.

TABLE 25. ADRENOCORTICAL RESPONSE TO SURGERY,[14] FREE AND CONJUGATED CORTISONE LEVELS IN PLASMA

Patient	Age	Preoperative		Postoperative					
				4 hours		24 hours		6 days	
		Free	Conj	Free	Conj	Free	Conj	Free	Con
A. W.	5 wks	7.5	7.1	12.5	10.0	8.0	5.0	6.9	5.0
B. D.	1 mo	2.1	0.0	3.8	0.2	1.3	0.0	—	—
V. G.	10 mo	2.2	0.1	4.0	2.8	1.8	0.0	—	—
J. L.	1 mo	1.5	0.0	2.0	0.0	—	—	—	—
G. N.	1 mo	2.33	0.0	8.2	1.0	0.5	0.0	—	—
P. C.	3 mo	5.9	1.33	7.5	3.33	6.1	0.83	—	—

The concentrating powers of the infant kidney are limited and there often occurs an increased plasma concentration of electrolytes and urea, which gradually declines as renal function becomes more efficient. It has been shown that the urea clearance and other function tests are impaired in the premature infant and, to a lesser extent, in the full-term infant.

Many pertinent aspects of preoperative and postoperative care in infants are described in the recent monograph by Kiesewetter.[8]

Endocrine Function

Adrenocortical activity. A relatively large amount of effort has been devoted to the study of adrenocortical function in infants, and some representative data are given in Table 25. The plasma levels of free hydrocortisone in the newborn are significantly lower than those in adults. This has been reported by various workers, and it has been confirmed in our own laboratory.[14] Furthermore, the level of hydrocortisone "conjugates" is extremely low in cord blood and in the newborn during the first few days of life.

Thyroid activity. The radioiodine uptake of normal newborn infants was measured by Van Middlesworth using 1 μc (microcurie) of I^{131}. The uptake of 7 infants was demonstrated to lie within the range of values which would be found in hyperthyroid adults.

The protein bound iodine level has been found to average 4.7 μg (micrograms) per cent at birth, rising gradually over the next few days.

Metabolic Response of Infants to Anesthesia and Operation

The metabolic response of the adult to injury has been outlined in Chapter 1. The

objective here will be to point out the particular effects of anesthesia-operation upon the metabolism of the newborn.

Problems with Anesthesia

The fact that the cardiorespiratory apparatus of the premature and even of the full term infant is highly susceptible to noxious influences was indicated earlier The breathing of the very small infant is often jerky and irregular, and the induction of anesthesia may be difficult for this reason Actually, much may be achieved merely with local anesthesia and a sugar or whisky teat pacifier, particularly is this mode of anesthesia adequate for body wall repairs such as small to moderate sized omphaloceles

When general anesthesia must be used, the apparatus and the anesthesiologist must be chosen with the patient in mind In our opinion in few other circumstances is the general anesthesiologist more likely to get into difficulty than in giving a small infant anesthesia for a thoracic procedure If the anesthetist has not had experience with infants, some one who has had such experience should be in attendance

We do not argue that one must choose for thoracic procedures a closely fitting mask without an endotracheal tube, or an endotracheal tube without a cuff, or an endotracheal tube with a cuff All three methods are in use, and the good anesthesiologist gets good results with whatever he chooses to employ It so happens that we are more accustomed to the use of an endotracheal tube without a cuff Open drop ether is a good anesthetic where judiciously used for procedures that do not require positive pressure —as with thoracic operations Cyclopropane is satisfactory for closed circuit anesthesia it permits rapid induction and rapid recovery, and a high concentration of oxygen can be used

Preanesthetic medication dosages are given in Figure 275

Body Temperatures during Anesthesia

The hazard of excessive hypothermia or of hyperthermia during anesthesia was emphasized by Bigler and McQuiston [1] Due to the aforementioned lability of the heat-regulating mechanisms, the infant may be subjected to wide swings in body temperature They found that infants under 6 months of

PREOPERATIVE MEDICATION CHILDREN S HOSPITAL OF PITTSBURGH*

Age	Wt /Lb.	Apothecary (Gr)			Metric (Mg.)		
		Morph.	Nemb	Scop.	Morph.	Nemb.	Scop.
0–2 mo	7–10	1/480	—	1/800	0 125	—	0 075
2–3	10–12	1/320	—	1/800	0 2	—	0 075
3–4	12–14	1/240	—	1/600	0 3	—	0 1
4–7	14–16	1/144	—	1/600	0 4	—	0 1
7–11	16–19	1/112	—	1/600	0 5	—	0 1
11–18	19–24	1/96	—	1/400	0 6	—	0 15
18–24	21–27	1/72	1/4	1/400	0 8	15	0 15
2–3 yr	27–30	1/64	1/4	1/400	1 0	15	0 15
3–5	30–40	1/48	ss	1/300	1 5	30	0 2
5–8	40–55	1/32	ss	1/300	2 0	30	0 2
8–10	55–65	1/24	i	1/200	2 5	60	0 3
10–12	65–80	1/16	i	1/200	4 0	60	0 3
12–14	80–90	1/12	iss	1/200	5 0	90	0 3
Over 14	90 +	1/8	iss	1/200	8 0	90	0 3

Fig 275 Great care is required in preparing the dosage of strong drugs for infants. (From KIESEWETTER, W B *Pre- and Postoperative Care in the Pediatric Surgical Patient* Chicago Year Book Publishers, Inc., 1956 as modified from LEIGH M D AND BELTON M. K. *Pediatric Anesthesia* New York, The Macmillan Company 1948)

age tended to develop subnormal temperatures during surgery, which had not seemed harmful In contrast, fever developed in over 62 per cent of their series of patients between the ages of 6 months and 13 years when they were not cooled A cold water mattress was found to be more efficient than ice bags in preventing fever

Metabolic effects (including acidosis) of anesthesia Bunker and his co-workers[2] investigated acid-base equilibria and certain other indices of metabolism in comparing ether with cyclopropane as an anesthetic for infants During *ether anesthesia,* infants under 1 year, unlike adults, regularly developed a moderate *respiratory acidosis* but no metabolic acidosis

In passing, it might be mentioned that during ether anesthesia the state of carbohydrate metabolism resembles in many respects that of uncontrolled diabetes mellitus

Other aspects of the response to surgery Aside from studies of the free and conjugated hydrocortisone levels in plasma before, during, and following surgery (Table 25), we have not done metabolic studies in infants and must turn to the literature It has been seen that the general pattern of the response of the plasma levels of free hydrocortisone in the newborn was similar to that in adults, but that the levels were lower in the infant, there is almost no conjugated hydrocortisone in the blood of the newborn (or in cord blood) [5]

Rickham[11] has recently reported in monograph form his detailed metabolic studies in 9 infants who underwent surgery In general the results reported do not appear to differ radically from those in adults except, perhaps, in respect to potassium metabolism The postoperative increase in potassium excretion so characteristic of the adult response was not observed in the newborn

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Chapter 21

Urologic Considerations of Special Interest

Certain problems in the field of urology hold particular interest for all physicians. Those to be discussed briefly are as follows: (1) Urinary calculi, (2) hematuria, (3) injuries to kidneys, ureters, bladder or urethra, (4) urinary retention, acute and chronic, and (5) ureterosigmoidostomy.

Urinary Calculi

While a definite set of circumstances can be predicted to result in a relatively large incidence of renal stones, by no means all stones can be explained on the basis of one or the other of the individual circumstances. In fact, the majority of renal stones have no obvious etiology and, indeed, where a predisposing situation exists there still is the question of precisely why calcium precipitates in some subjects and not in others.

Among the common and important predisposing factors may be listed the following: (1) prolonged bed rest (calcium is mobilized when the subject is immobilized), (2) hyperparathyroidism (calcium is mobilized in large amounts), (3) bacterial infection (certain organisms particularly predispose to renal stone formation), (4) urinary tract obstruction (urinary stagnation and increased incidence of infection), (5) dehydration (important in relatively few), and (6) metabolic (organic) dysfunction (uric acid or cystine calculi).

From this list it may be seen that calcium mobilization, urinary tract infection and urinary tract obstruction are particularly important in stone formation. Calcium is a component of most primary urinary calculi.

Physical Factors in Stone Formation[5]

It has been pointed out that every specimen of urine contains stone-forming elements such as uric acid and calcium oxalate. Their solubility in urine depends upon: (1) The pH of the urine. At pH 5 pure uric acid is present to the point of saturation, at pH 7 the urine is supersaturated with calcium oxalate. (2) The presence of other electrolytes in the urine, such as sodium phosphate. (3) The presence of certain nonelectrolytes in the urine. For example, the solubility of calcium oxalate in water is doubled by adding urea.

Protective effect of urinary colloids. Great interest has developed recently in the protective rôle of the urinary colloids as regards stone formation. These substances normally consist of mucin, nucleic acid, chondroitin sulfuric acid and a complex nitrogen containing carbohydrate. Precipitation of the urinary colloids may result in stone formation. It has been shown that the total quantity of proteins and other particles of colloidal size in the urine of patients with calculous disease is 3 to 13 times greater than in normal urine. Some of the factors which may influence the quantity of urinary mucoproteins were considered by Boyce, Garvey, and Norfleet.[1, 2] Two patients with hyperparathyroidism due to functioning adenomas were found to have the highest concentrations of urinary mucoproteins in their clinical series. It was felt that the most important single factor influencing the turbidity of urine was the pH.

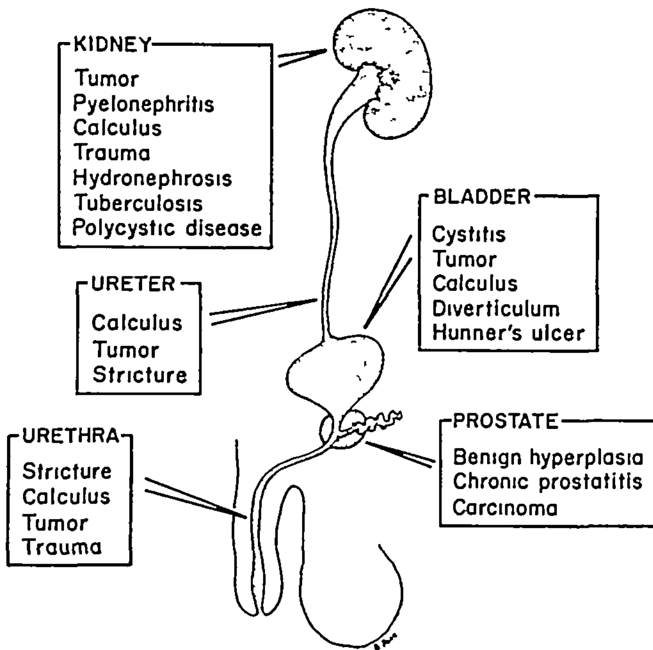


Fig 276 The cause of gross hematuria should always be determined

Prevention of Stone Formation

The initial step in prophylaxis is that of avoiding the conditions which predispose to stone formation In patients who have already formed one or more stones, certain special preventive measures may be tried Cystine stones can be prevented—and perhaps even reabsorbed—by reducing dietary protein intake and by giving alkalies to keep the urine constantly alkaline The prevention of calcium and phosphate stone recurrence is not as successful The use of hyaluronidase, acetylsalicylic acid, irrigating solutions, and vitamin A have been tried with inconclusive results The incidence of recurrence of renal calculi is approximately 30 per cent

Hematuria

The presence of blood in the urine may be so limited that microscopic means are required for its detection In contrast, urinary tract bleeding may be so extensive as to represent virtually pure blood Many of the same processes which cause microscopic hematuria initially may lead to gross hematuria later Some of the more important causes of hematuria are shown in Figure 276

The more common causes of gross hematuria arising in the kidney are tumor, infection, calculus, and trauma In the ureter, calculi represent by far the most prominent cause In the bladder, cystitis and tumor are frequent, whereas calculi far less often give rise to gross bleeding Prostatic hypertrophy, infection, or malignancy may occasion bleeding In the urethra, strictures and calculi produce bleeding most frequently

All significant hematuria should be carefully studied by means of intravenous pyelography, cystoscopy, and retrograde pyelography Urinalyses should be repeated until the hematuria has been explained or the urine is clear of even microscopic hematuria

Urinary Tract Injuries

The Kidney

The possibility of renal injury should be suggested by the history of circumstances that might have occasioned such injury, by physical examination, by urinalyses which shows red cells, and by urography The intravenous pyelogram may reveal extravasation of the radiopaque medium into the perirenal tissues

Management If hemorrhage or extravasation of radiopaque medium should force exploration of the involved kidney, one may be faced with the decision of whether or not to do a nephrectomy As a rule, conservatism is greatly to be desired The bleeding can often be stopped, the parts of the kidney sutured together, and the area drained All this may result in a functioning kidney Such a procedure recently saved renal function for an individual who sustained multiple gunshot injuries—for the ureter to the opposite kidney was later found to have been severed and after a number of weeks that kidney had to be removed In a few instances uncontrollable primary or secondary hemorrhage may require ne-

phrectomy but this should never be done electively unless the kidney is obviously mutilated beyond repair If one kidney is to be removed, it is always desirable to have proved function of the opposite organ by urography, rather than to depend upon simple palpation to establish its presence

Ureter

Many devices and technics have been proposed with which to salvage a damaged, severed, or ligated ureter By and large, however, permanent success is uncommon unless the ureter proximal to the injury can be implanted into the bladder To implant the ureter into the colon, to anastomose it over a small T tube or ureteral catheter or to perform cutaneous ureterostomy, all too often may result in ureteral stricture, hydronephrosis infection perhaps stone formation—and eventual loss of the kidney Nephrectomy is the final outcome of most ureteral injuries which occur at a level which precludes ureterocystostomy However, in the future such kidneys may be transplanted to the pelvis the renal vessels being anastomosed to the iliac vessels and the short ureter implanted into the bladder

Bladder

Bladder injuries are for the most part readily diagnosed and readily treated The injection of a measured volume of saline per urethral catheter, a cystogram, or the injection of fluorescein per catheter and its detection in peripheral blood have all been used to demonstrate bladder rupture The first two are generally used and are usually satisfactory

Suprapubic cystostomy with repair of the bladder injury with chromic catgut is indicated. Drainage is instituted as deemed necessary, for extravasated urine produces a particularly serious type of necrotizing inflammation (Fig. 277)



Fig 277 Result of urethral stricture with urinary extravasation. When urine extravasates, a particularly vicious inflammatory process may be produced. This patient sustained rupture of the urethra.

Urethra

Injuries to the urethra are likely to occur in association with fractures of the pelvis or in association with strictures, either spontaneously or during attempts at dilatation or passage of a catheter When rupture or tearing of the urethra does occur, it is generally desirable to perform cystostomy and to drain adequately This prevents further tissue damage by extravasated urine Healing of the urethra itself is facilitated if a Foley indwelling or other catheter can be inserted (from bladder outward at operation if necessary) to serve as a scaffold during mucosal regeneration

Urinary Retention: Acute and Chronic

Acute Urinary Retention

Following many operations the patient, especially if a male, may not be able to void for hours, days or even weeks When this follows upper abdominal or thoracic procedures it is usually assumed that the normal neuromuscular processes of micturition have been interrupted and that time is required for these pathways to regain normal function However operations which are particularly apt to be associated with inability to void are those involving the perineum i e, hemorrhoidectomy Here the postoperative pain may produce reflex spasm which the patient cannot voluntarily relax. Of course acute urinary retention may

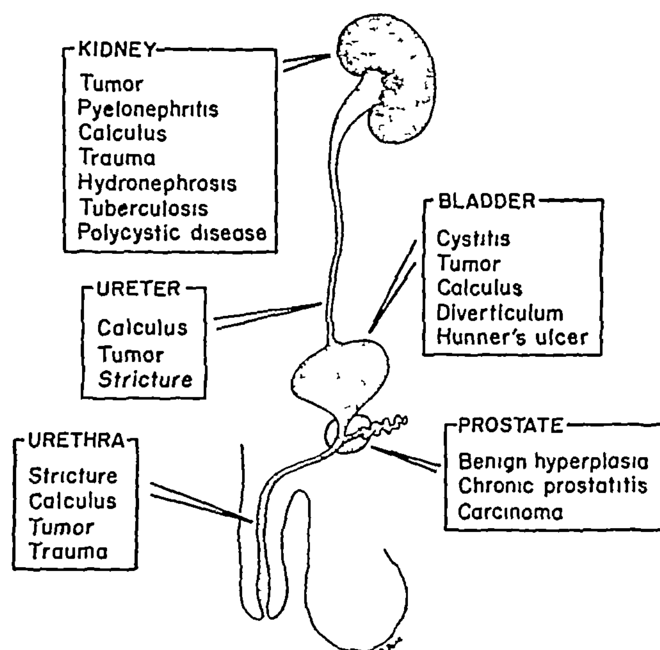


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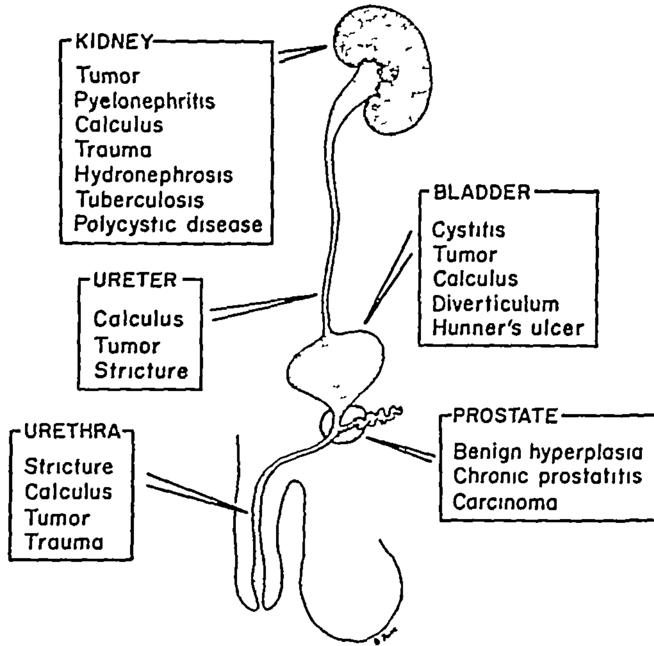


Fig 276 The cause of gross hematuria should always be determined

Prevention of Stone Formation

The initial step in prophylaxis is that of avoiding the conditions which predispose to stone formation In patients who have already formed one or more stones, certain special preventive measures may be tried Cystine stones can be prevented—and perhaps even reabsorbed—by reducing dietary protein intake and by giving alkalies to keep the urine constantly alkaline The prevention of calcium and phosphate stone recurrence is not as successful The use of hyaluronidase, acetylsalicylic acid, irrigating solutions, and vitamin A have been tried with inconclusive results The incidence of recurrence of renal calculi is approximately 30 per cent

Hematuria

The presence of blood in the urine may be so limited that microscopic means are required for its detection In contrast, urinary tract bleeding may be so extensive as to represent virtually pure blood Many of the same processes which cause microscopic hematuria initially may lead to gross hematuria later Some of the more important causes of hematuria are shown in Figure 276

The more common causes of gross hematuria arising in the kidney are tumor, infection, calculus, and trauma In the ureter, calculi represent by far the most prominent cause In the bladder, cystitis and tumor are frequent, whereas calculi far less often give rise to gross bleeding Prostatic hypertrophy, infection, or malignancy may occasion bleeding In the urethra, strictures and calculi produce bleeding most frequently

All significant hematuria should be carefully studied by means of intravenous pyelography, cystoscopy, and retrograde pyelography Urinalyses should be repeated until the hematuria has been explained or the urine is clear of even microscopic hematuria

Urinary Tract Injuries

The Kidney

The possibility of renal injury should be suggested by the history of circumstances that might have occasioned such injury, by physical examination, by urinalyses which shows red cells, and by urography The intravenous pyelogram may reveal extravasation of the radiopaque medium into the perirenal tissues

Management If hemorrhage or extravasation of radiopaque medium should force exploration of the involved kidney, one may be faced with the decision of whether or not to do a nephrectomy As a rule, conservatism is greatly to be desired The bleeding can often be stopped, the parts of the kidney sutured together, and the area drained All this may result in a functioning kidney Such a procedure recently saved renal function for an individual who sustained multiple gunshot injuries—for the ureter to the opposite kidney was later found to have been severed and after a number of weeks that kidney had to be removed In a few instances uncontrollable primary or secondary hemorrhage may require ne-

phrectomy but this should never be done electively unless the kidney is obviously mutilated beyond repair If one kidney is to be removed, it is always desirable to have proved *function of the opposite* organ by urography, rather than to depend upon simple palpation to establish its presence

Ureter

Many devices and technics have been proposed with which to salvage a damaged, severed, or ligated ureter By and large, however, permanent success is uncommon unless the ureter proximal to the injury can be implanted into the bladder To implant the ureter into the colon, to anastomose it over a small T tube or ureteral catheter, or to perform cutaneous ureterostomy, all too often may result in ureteral stricture, hydronephrosis, infection, perhaps stone formation—and eventual loss of the kidney Nephrectomy is the final outcome of most ureteral injuries which occur at a level which precludes ureterocystostomy However, in the future such kidneys may be transplanted to the pelvis, the renal vessels being anastomosed to the iliac vessels and the short ureter implanted into the bladder

Bladder

Bladder injuries are for the most part readily diagnosed and readily treated. The injection of a measured volume of saline per urethral catheter, a cystogram, or the injection of fluorescein per catheter and its detection in peripheral blood have all been used to demonstrate bladder rupture. The first two are generally used and are usually satisfactory

Suprapubic cystostomy with repair of the bladder injury *with chromic catgut is indicated* Drainage is instituted as deemed necessary, for extravasated urine produces a particularly serious type of necrotizing inflammation (Fig 277)



Fig 277 Result of urethral stricture with urinary extravasation. When urine extravasates, a particularly vicious inflammatory process may be produced This patient sustained rupture of the urethra.

Urethra

Injuries to the urethra are likely to occur in association with fractures of the pelvis or in association with strictures, either spontaneously or during attempts at dilatation or passage of a catheter When rupture or tearing of the urethra does occur, it is generally desirable to perform cystostomy and to drain adequately This *prevents further* tissue damage by extravasated urine Healing of the urethra itself is facilitated if a Foley indwelling or other catheter can be inserted (from bladder outward at operation *if necessary) to serve as a scaffold* during mucosal regeneration

Urinary Retention: Acute and Chronic

Acute Urinary Retention

Following many operations the patient, especially if a male may not be able to void for hours days or even weeks When this follows upper abdominal or thoracic procedures it is usually assumed that the normal neuromuscular processes of micturition have been interrupted and that time is required for these pathways to regain normal function However, operations which are particularly apt to be associated with inability to void are those involving the perineum i.e hemorrhoidectomy Here the postoperative pain may produce reflex spasm which the patient cannot voluntarily relax Of course acute *urinary retention* may

occur when no operation has been performed, in conditions such as prostatic hypertrophy or urethral stricture

In most instances of acute urinary retention one first attempts to pass a urethral catheter If this cannot be done, the suprapubic cystostomy must often be resorted to In some patients the bladder sphincter can be caused to relax by placing the penis in warm water, standing the male subject up, by allowing the patient to sit on the commode, by the sound of running water or by the use of cholinergic drugs

The indwelling catheter We know surgical services on which almost every male patient has an indwelling Foley (self-retaining) catheter inserted prior to, during, or shortly following surgery This is a "routine" and has no relation to whether or not the individual might have been able to void

We are opposed to the routine use of an indwelling catheter following surgery To begin with, most surgeons would (if operated upon themselves) probably elect to attempt to void before catheterization was resorted to Hence, for reasons of both comfort and peace of mind, voiding is superior to catheterization Second—and more important—bladder and urethral infections are increased by the promiscuous use of indwelling catheters

Our practice is to remove the catheter the first time catheterization is required If it must be repeated, then a Foley catheter is used and left in until the patient is out of bed and ambulatory When catheters are required for prolonged periods they should be changed with reasonable frequency to diminish incrustation and stone formation

Chronic Urinary Retention

Prostatic hypertrophy is a most frequent cause of chronic urinary retention During the past 20 years much progress has been made in reducing the morbidity and mortality associated with the treatment of "prostatism" Essentially, long-standing incomplete obstruction of the urethra results in urinary retention, bladder distention, and infection

Effect of back pressure on the kidneys[4] As the obstruction increases, the accumulation of urine in the bladder raises intravesical pressure, and there results an increase in intraureteral and intrapelvic pressure In turn, this pressure is transmitted to the infundibula, calices, and tubules of the nephrons Since effective glomerular filtration pressure is the difference between the intravascular hydrostatic pressure, on the one hand, and the sum of the osmotic pressure of the plasma proteins and the intrarenal tissue pressure, on the other, any increase in renal tissue pressure produced by urinary retention will result in decreased glomerular filtration Glomerular filtration will be impaired further because of decreased blood flow, as a result of compression of the blood vessels by the increased intrarenal tissue pressure Tubular function will be disturbed also because of a decrease in peritubular blood flow, which is due to compression of the vessels by increased intrarenal pressure

Hence, it is apparent that sustained hydrostatic back pressure due to urinary tract obstruction has multiple deleterious effects upon renal physiology If complete obstruction persists for long, as following ligation of a ureter, renal function will cease on the involved side, that is, the kidney will be destroyed In contrast, if obstruction is relieved promptly, renal function may be largely restored

To return to chronic, incomplete lower urinary tract obstruction, anemic and pressure atrophy of renal tubules will be followed by glomerular destruction, until finally little functioning parenchyma remains Moreover, the degree of renal destruction is essentially proportional to the duration and the degree of obstruction Following bladder decompression, one may expect improvement in both glomerular and tubular function over the next few weeks, provided irreversible structural changes leading to intractable renal failure have not occurred

The *electrolyte disorders* which develop in the presence of urinary tract obstruction depend, again, upon the duration and degree of obstruction. Of course, abrupt and complete obstruction results in clinical uremia after a few days. Brief but incomplete obstruction may produce little more than azotemia without significant change in the plasma electrolytes. Chronic obstruction with the almost inevitable infection, however, results in progressive renal damage and insufficiency. Almost invariably the carbon dioxide combining power declines, with or without an early decline in blood pH. lowered "CO_2" is due in part to the accumulation of fixed acid radicals such as sulfates and phosphates—that is it is a pulmonary compensation phenomenon (Fig. 194). Acidotic breathing and the other familiar symptomatology of chronic renal failure eventually ensue.

Immediate versus gradual bladder compression. For many years it was considered hazardous to decompress the chronically distended bladder abruptly lest anuria or various forms of "collapse" be precipitated. More recently this view has been abandoned in favor of immediate and total decompression, since few report more than temporary albuminuria and microscopic hematuria due presumably to reactive renal congestion.

Pathophysiology of Ureterosigmoidostomy

Radical cystectomy for cancer and other conditions has required implantation of the ureters in the skin or more frequently, in the colon or an isolated ileal loop. Creevy[3] has inquired into whether the prognosis of ureterosigmoidostomy itself quite apart from that of a cancer is good enough to support the use of this procedure other less radical bladder resection for cancer, with preservation of normal continuity of the urinary tract, might result in a greater salvage of happy life, if the complications of ureterosigmoidostomy are too great. While patients have been reported who survived many years following ureterosigmoidostomy for exstrophy of the bladder (in one instance, 43 years), it is not known what proportion of the cases done have this favorable a longevity.

Hazards of ureterosigmoidostomy.[3] It has been pointed out that there are many objections to all types of anastomoses between the ureters and the bowel. Paramount is the incidence of ascending renal infection following exposure of the normally sterile kidneys to the reflux of colon contents. The longer the anastomosis exists, the higher the incidence of serious infection of the kidneys, which ranges from 30 to 70 per cent of cases in various reported series. For example, only 30 per cent of patients may still exhibit a normal urographic appearance as early as 18 months following the operation. Clearly, the infection and perhaps a degree of hydronephrosis from ureteral stricture take a heavy toll of functioning renal parenchyma (Fig. 278).

Mechanism of hyperchloremic acidosis following ureterosigmoidostomy. For some time it was believed that the hyperchloremic acidosis which gradually appears over the months in many patients following ureterosigmoidostomy was due to excessive reabsorption of urinary chlorides from the colon. However this did not explain the often late appearance of this phenomenon. It has since

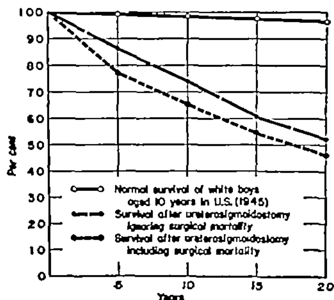


Fig. 278. Prognosis for life following ureterosigmoidostomy for nonmalignant disease. (From Creevy, C. D.: Facts about ureterosigmoidostomy. J. A. M. A., 151: 120, 1953.)

been appreciated that, in addition to the reabsorption of urinary chlorides from the bowel, a diminished renal function is also important That is, normally functioning kidneys are able to re-excrete the chlorides reabsorbed from the bowel—and at a rate which prevents hyperchloremia from occurring As renal damage due to chronic infection and hydronephrosis develops, however, the rate of chloride excretion diminishes and chloride retention occurs The alkali reserve is gradually depleted by combining with the fixed acid chloride radical, and metabolic acidosis results

In summary, while hyperchloremic acidosis due to chloride reabsorption probably can develop in the absence of renal impairment, the latter is doubtless a complementing factor in most cases The azotemia which may develop following ureteroenteric anastomoses may be due to absorption not only of urea but also of ammonia from the bowel To minimize the chemical derangements due in part to reabsorption of various urinary constituents, it has been recommended (1) that a high fluid intake be urged to dilute the urinary constituents in the bowel so as to diminish rates of absorption, (2) that the rectum or isolated pouch be emptied frequently (every hour or so) to reduce the length of time that the chloride ion is in contact with the mucosal surface, and (3) that the length of bowel that the urine must traverse be minimized Sodium bicarbonate should be given by mouth to reduce the tendency toward acidosis

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